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(54) Title: CRYSTALLINE FORMS OF THERAPEUTICALLY ACTIVE COMPOUNDS AND USE THEREOF

(57) Abstract: Provided are crystalline forms of 2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{ [2-(trifluoromethyl)pyridin-4-yl]amino }-1, 3, 5-triazin-2-yl)amino]propan-2-ol(COMPOUND 3), 2-methyl-1-[(4- [6-(trifluoromethyl)pyridin-2-yi]-6-{ [2-(trifluoromethyl)pyridin-4- yl]amino }-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1) and use thereof.

# CRYSTALLINE FORMS OF THERAPEUTICALLY ACTIVE COMPOUNDS AND USE THEREOF

Isocitrate dehydrogenases (IDHs) catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (*i.e.*, α-ketoglutarate). These enzymes belong to two distinct subclasses, one of which utilizes NAD(+) as the electron acceptor and the other NADP(+). Five isocitrate dehydrogenases have been reported: three NAD(+)-dependent isocitrate dehydrogenases, which localize to the mitochondrial matrix, and two NADP(+)-dependent isocitrate dehydrogenases, one of which is mitochondrial and the other predominantly cytosolic. Each NADP(+)-dependent isozyme is a homodimer.

IDH2 (isocitrate dehydrogenase 2 (NADP+), mitochondrial) is also known as IDH; IDP; IDHM; IDPM; ICD-M; or mNADP-IDH. The protein encoded by this gene is the NADP(+)-dependent isocitrate dehydrogenase found in the mitochondria. It plays a role in intermediary metabolism and energy production. This protein may tightly associate or interact with the pyruvate dehydrogenase complex. Human IDH2 gene encodes a protein of 452 amino acids. The nucleotide and amino acid sequences for IDH2 can be found as GenBank entries NM_002168.2 and NP_002159.2 respectively. The nucleotide and amino acid sequence for human IDH2 are also described in, *e.g.,* Huh *et al*., Submitted (NOV-1992) to the EMBL/GenBank/DDBJ databases; and The MGC Project Team, Genome Res. 14:2121-2127(2004).

Non-mutant, *e.g.,* wild type, IDH2 catalyzes the oxidative decarboxylation of isocitrate to α-ketoglutarate (α-KG) thereby reducing $NAD^+$ ($NADP^+$) to NADH (NADPH), *e.g.,* in the forward reaction:

Isocitrate + $NAD^+$ ($NADP^+$) → α-KG + $CO_2$ + NADH (NADPH) + $H^+$.

It has been discovered that mutations of IDH2 present in certain cancer cells result in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH2. The production of 2HG is believed to contribute to the formation and progression of cancer (Dang, L et al, Nature 2009, 462:739-44).

The inhibition of mutant IDH2 and its neoactivity is therefore a potential therapeutic treatment for cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell

lymphoma). Accordingly, there is an ongoing need for inhibitors of IDH2 mutants having alpha hydroxyl neoactivity.

PCT Publication No. WO 2013/102431 and US Publication No. US 2013/0190287 hereby incorporated by reference in their entirety, disclose compounds that inhibit IDH2 mutants (*e.g.*, IDH2R140Q and IDH2R172K). For example, the compound 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol, and the mesylate salt thereof is an inhibitor of mutant IDH2. These applications additionally disclose methods for the preparation of inhibitors of mutant IDH2, pharmaceutical compositions containing these compounds, and methods for the therapy of diseases, disorders, or conditions (*e.g.*, cancer) associated with overexpression and/or amplification of mutant IDH2. These applications describe the synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol, which results in an unpredictable mixture of amorphous and crystalline forms. These applications do not disclose specific crystalline forms of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol.

A primary concern for the manufacture of large-scale pharmaceutical compositions is that the active ingredient should have a stable crystalline morphology to ensure consistent processing parameters and pharmaceutical quality. The active ingredient must possess acceptable properties with respect to hygroscopicity, solubility, and stability, which can be consistently reproduced despite the impact of various environmental conditions such as temperature and humidity. If an unstable crystalline form is used, crystal morphology may change during manufacture and/or storage resulting in quality control problems, and formulation irregularities. Such a change may affect the reproducibility of the manufacturing process and thus lead to pharmaceutical formulations that do not meet the high quality and stringent requirements imposed on formulations of pharmaceutical compositions.

When a compound crystallizes from a solution or slurry, it may crystallize with different spatial lattice arrangements, a property referred to as "polymorphism." Each of the crystal forms is a "polymorph." While polymorphs of a given substance have the same chemical composition, they may differ from each other with respect to one or more physical properties, such as

solubility and dissociation, true density, melting point, crystal shape, compaction behavior, flow properties, and/or solid state stability.

The polymorphic behavior of pharmaceutically active substances is of great importance in pharmacy and pharmacology. The differences in physical properties exhibited by polymorphs affect practical parameters such as storage stability, compressibility and density (important in pharmaceutical composition manufacturing), and dissolution rates (an important factor in determining bio-availability of an active ingredient). Differences in stability can result from changes in chemical reactivity (e.g., differential oxidation, such that a dosage form discolors more rapidly when it is one polymorph than when it is another polymorph) or mechanical changes (e.g., tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g., tablets of one polymorph are more susceptible to breakdown at high humidity than another polymorph). In addition, the physical properties of the crystal may be important in processing: for example, one polymorph might be more likely to form solvates that cause the solid form to aggregate and increase the difficulty of solid handling, or might be difficult to filter and wash free of impurities (i.e., particle shape and size distribution might be different between one polymorph relative to other).

While pharmaceutical formulations having improved chemical and physical properties are desired, there is no predictable means for preparing new crystalline forms (e.g., polymorphs) of existing molecules for such formulations. There is a need for crystalline forms of inhibitors of mutant IDH2 that possess consistent physical properties over the range of environments that may be encountered during pharmaceutical formulation manufacturing and storage. Such crystalline forms would have utility in treating a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) characterized by the presence of a mutant allele of IDH2, as well as having properties suitable for large-scale manufacturing and formulation.

## SUMMARY OF INVENTION

Disclosed herein are crystalline forms of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1). Also disclosed herein are crystalline forms of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-

yl)amino]propan-2-ol (COMPOUND 3).These forms have properties advantageous for large-scale manufacturing, pharmaceutical formulation, and storage.

Also disclosed herein are processes for the synthesis of crystalline forms of COMPOUND 1 and COMPOUND 3. Also disclosed herein is the pharmaceutical use of crystalline forms of COMPOUND 1 and COMPOUND 3 as mutant IDH2 inhibitors.

## BRIEF DESCRIPTION OF THE DRAWINGS

FIGURE 1 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 1.

FIGURE 2 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 2.

FIGURE 3 is a differential scanning calorimetry (DSC) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 2.

FIGURE 4 is a thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 2.

FIGURE 5 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 3.

FIGURE 6 is a differential scanning calorimetry (DSC) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 3.

FIGURE 7 is a thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 3.

FIGURE 8 is a dynamic vapor sorption (DVS) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 3.

FIGURE 9 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 4.

FIGURE 10 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 4.

FIGURE 11 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 5.

FIGURE 12 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 5.

FIGURE 13 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 6.

FIGURE 14 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 6.

FIGURE 15 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 7.

FIGURE 16 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 7.

FIGURE 17 is a X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 8.

FIGURE 18 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 8.

FIGURE 19 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 9.

FIGURE 20 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 9.

FIGURE 21 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 10.

FIGURE 22 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 10.

FIGURE 23 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 11.

FIGURE 24 is a differential scanning calorimetry (DSC) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 11.

FIGURE 25 is a thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 11.

FIGURE 26 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 12.

FIGURE 27 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 12.

FIGURE 28 is a X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 13.

FIGURE 29 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 13.

FIGURE 30 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 14.

FIGURE 31 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 14.

FIGURE 32 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 15.

FIGURE 33 is a differential scanning calorimetry (DSC) and thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 15.

FIGURE 34 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16.

FIGURE 35 is a differential scanning calorimetry (DSC) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16.

FIGURE 36 is a thermal gravimetric analysis (TGA) profile of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16.

FIGURE 37 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 17.

FIGURE 38 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 18.

FIGURE 39 is an X-ray powder diffractogram (XRPD) of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 19.

## DETAILED DESCRIPTION OF THE INVENTION

The details of construction and the arrangement of components set forth in the following description or illustrated in the drawings are not meant to be limiting. Other embodiments and different ways to practice the invention are expressly included. Also, the phraseology and terminology used herein is for the purpose of description and should not be regarded as limiting. The use of "including," "comprising," or "having," "containing", "involving", and variations thereof herein, is meant to encompass the items listed thereafter and equivalents thereof as well as additional items.

**Definitions:**

As used above, and throughout the description of the invention, the following terms, unless otherwise indicated, shall be understood to have the following meanings.

"Free Base" is meant to describe 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3).

"Mesylate Salt" is meant to describe 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1).

"Form 1" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 1" are used interchangeably, and describe Form 1 COMPOUND 3, as synthesized in Example 3, in the Examples section below, and as described below, and represented by data shown in FIG. 1.

"Form 2" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 2" are used interchangeably, and describe Form 2 of COMPOUND 3, as synthesized in Example 4, in the Examples section below, and as described below, and represented by data shown in FIGS. 2, 3, and 4.

"Form 3" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate

Form 3" are used interchangeably, and describe Form 3 of COMPOUND 1, as synthesized in Example 6, in the Examples section below, and as described below, and represented by data shown in FIGS. 5, 6, 7, and 8.

"Form 4" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 4" are used interchangeably, and describe Form 4 of COMPOUND 1, as synthesized in Example 7, in the Examples section below, and as described below, and represented by data shown in FIGS. 9 and 10.

"Form 5" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 5" are used interchangeably, and describe Form 5 of COMPOUND 1, as synthesized in Example 8, in the Examples section below, and as described below, and represented by data shown in FIGS. 11 and 12.

"Form 6" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 6" are used interchangeably, and describe Form 6 of COMPOUND 1, as synthesized in Example 9, in the Examples section below, and as described below, and represented by data shown in FIGS. 13 and 14.

"Form 7" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 7" are used interchangeably, and describe Form 7 of COMPOUND 1, as synthesized in Example 10, in the Examples section below, and as described below, and represented by data shown in FIGS. 15 and 16.

"Form 8" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 8" are used interchangeably, and describe Form 8 of COMPOUND 1, as synthesized in Example 11, in the Examples section below, and as described below, and represented by data shown in FIGS. 17 and 18.

"Form 9" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 9" are used interchangeably, and describe Form 9 of COMPOUND 1, as synthesized in

Example 12, in the Examples section below, and as described below, and represented by data shown in FIGS. 19 and 20.

"Form 10" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 10" are used interchangeably, and describe Form 10 of COMPOUND 1, as synthesized in Example 13, in the Examples section below, and as described below, and represented by data shown in FIGS. 21 and 22.

"Form 11" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 11" are used interchangeably, and describe Form 11 of COMPOUND 1, as synthesized in Example 14, in the Examples section below, and as described below, and represented by data shown in FIGS. 23, 24, and 25.

"Form 12" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 12" are used interchangeably, and describe Form 12 of COMPOUND 1, as synthesized in Example 15, in the Examples section below, and as described below, and represented by data shown in FIGS. 26 and 27.

"Form 13" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 13" are used interchangeably, and describe Form 13 of COMPOUND 1, as synthesized in Example 16, in the Examples section below, and as described below, and represented by data shown in FIGS. 28 and 29.

"Form 14" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 14" are used interchangeably, and describe Form 14 of COMPOUND 1, as synthesized in Example 17, in the Examples section below, and as described below, and represented by data shown in FIGS. 30 and 31.

"Form 15" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 15" are used interchangeably, and describe Form 15 of COMPOUND 1, as synthesized in

Example 18, in the Examples section below, and as described below, and represented by data shown in FIGS. 32 and 33.

"Form 16" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16" are used interchangeably, and describe Form 16 COMPOUND 3, as synthesized in Example 2, in the Examples section below, and as described below, and represented by data shown in FIGS. 34, 35 and 36.

"Form 17" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16" are used interchangeably, and describe Form 16 COMPOUND 3, as synthesized in Example 20, in the Examples section below, and as described below, and represented by data shown in FIG. 37.

"Form 18" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16" are used interchangeably, and describe Form 16 COMPOUND 3, as synthesized in Example 21, in the Examples section below, and as described below, and represented by data shown in FIG. 38.

"Form 19" or "2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 16" are used interchangeably, and describe Form 16 COMPOUND 3, as synthesized in Example 22, in the Examples section below, and as described below, and represented by data shown in FIG. 39.

As used herein, "crystalline" refers to a solid having a highly regular chemical structure. In particular, a crystalline Free Base or Mesylate Salt may be produced as one or more single crystalline forms of the Free Base or Mesylate Salt. For the purposes of this application, the terms "crystalline form", "single crystalline form" and "polymorph" are synonymous; the terms distinguish between crystals that have different properties (e.g., different XRPD patterns and/or different DSC scan results). The term "polymorph" includes pseudopolymorphs, which are typically different solvates of a material, and thus their properties differ from one another. Thus, each distinct polymorph and pseudopolymorph of the Free Base or Mesylate Salt is considered to be a distinct single crystalline form herein.

"Substantially crystalline" refers to forms that may be at least a particular weight percent crystalline. Particular weight percentages are 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%,

or any percentage between 10% and 100%. In some embodiments, substantially crystalline refers to a Free Base of Mesylate Salt that is at least 70% crystalline. In other embodiments, substantially crystalline refers to a Free Base of Mesylate Salt that is at least 90% crystalline.

As used herein, the terms "isolated" refers to forms that may be at least a particular weight percent of a particular crystalline form of COMPOUND 1 or COMPOUND 3. Particular weight percentages are 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 90% and 100%.

The term "solvate or solvated" means a physical association of a compound, including a crystalline form thereof, of this invention with one or more solvent molecules. This physical association includes hydrogen bonding. In certain instances the solvate will be capable of isolation, for example when one or more solvent molecules are incorporated in the crystal lattice of the crystalline solid. "Solvate or solvated" encompasses both solution-phase and isolable solvates. Representative solvates include, for example, a hydrate, ethanolates or a methanolate.

The term "hydrate" is a solvate wherein the solvent molecule is $H_2O$ that is present in a defined stoichiometric amount, and may for example, include hemihydrate, monohydrate, dihydrate, or trihydrate.

The term "mixture" is used to refer to the combined elements of the mixture regardless of the phase-state of the combination (e.g., liquid or liquid/ crystalline).

The term "seeding" is used to refer to the addition of a crystalline material to initiate recrystallization or crystallization.

The term "antisolvent" is used to refer to a solvent in which compounds, including a crystalline forms thereof, are poorly soluble.

As used herein, the term “about” means approximately, in the region of, roughly, or around. When the term “about” is used in conjunction with a numerical range, it modifies that range by extending the boundaries above and below the numerical values set forth. In general, the term “about” is used herein to modify a numerical value above and below the stated value by a variance of 10%.

As used herein, the term “elevated levels of 2HG” means 10%, 20% 30%, 50%, 75%, 100%, 200%, 500% or more 2HG then is present in a subject that does not carry a mutant IDH2 allele. The term “elevated levels of 2HG” may refer to the amount of 2HG within a cell, within a tumor, within an organ comprising a tumor, or within a bodily fluid.

The term "bodily fluid" includes one or more of amniotic fluid surrounding a fetus, aqueous humour, blood (*e.g.,* blood plasma), serum, Cerebrospinal fluid, cerumen, chyme, Cowper's fluid, female ejaculate, interstitial fluid, lymph, breast milk, mucus (*e.g.,* nasal drainage or phlegm), pleural fluid, pus, saliva, sebum, semen, serum, sweat, tears, urine, vaginal secretion, or vomit.

As used herein, the terms "inhibit" or "prevent" include both complete and partial inhibition and prevention. An inhibitor may completely or partially inhibit the intended target.

The term "treat" means decrease, suppress, attenuate, diminish, arrest, or stabilize the development or progression of a disease/disorder (i.e., a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma)), lessen the severity of the disease/disorder (i.e., a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma)) or improve the symptoms associated with the disease/disorder (i.e., a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma)).

As used herein, an amount of a compound, including a crystalline form thereof, effective to treat a disorder, or a "therapeutically effective amount" refers to an amount of the compound, including a crystalline form thereof, which is effective, upon single or multiple dose administration to a subject, in treating a cell, or in curing, alleviating, relieving or improving a subject with a disorder beyond that expected in the absence of such treatment.

As used herein, the term "subject" is intended to mean human. Exemplary human subjects include a human patient (referred to as a patient) having a disorder, e.g., a disorder described herein or a normal subject.

**Crystalline Forms**

Provided are crystalline forms of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1). Also provided are crystalline forms of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3).

In one embodiment, COMPOUND 1 is a single crystalline form, or any one of the single crystalline forms described herein. Also provided are pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier or diluent; and COMPOUND 1, wherein COMPOUND 1 is a single crystalline form, or any one of the crystalline forms being described herein. Also provided are uses of COMPOUND 1, wherein COMPOUND 1 is a single crystalline form, or any one of the single crystalline forms described herein, to prepare a pharmaceutical composition.

In one embodiment, COMPOUND 3 is a single crystalline form, or any one of the single crystalline forms described herein. Also provided are pharmaceutical compositions comprising at least one pharmaceutically acceptable carrier or diluent; and COMPOUND 3, wherein COMPOUND 3 is a single crystalline form, or any one of the crystalline forms being described herein. Also provided are uses of COMPOUND 3, wherein COMPOUND 3 is a single crystalline form, or any one of the single crystalline forms described herein, to prepare a pharmaceutical composition.

Also provided are methods of treating a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) characterized by the presence of a mutant allele of IDH2 comprising the step of administering to subject in need thereof (a) a single crystalline form of COMPOUND 1 or COMPOUND 3, or (b) a pharmaceutical composition comprising (a) and a pharmaceutically acceptable carrier. In one embodiment, the single crystalline form in (a) is any percentage between 90% and 100% pure.

Provided herein is an assortment of characterizing information to describe the crystalline forms of COMPOUND 1 and COMPOUND 3. It should be understood, however, that not all such information is required for one skilled in the art to determine that such particular form is present in a given composition, but that the determination of a particular form can be achieved using any portion of the characterizing information that one skilled in the art would recognize as sufficient for establishing the presence of a particular form, *e.g.*, even a single distinguishing peak can be sufficient for one skilled in the art to appreciate that such particular form is present.

Crystalline forms of COMPOUND 1 have physical properties that are suitable for large scale pharmaceutical formulation manufacture. Many of the crystalline forms of COMPOUND 1 described herein exhibit high crystallinity, high melting point, and limited occluded or solvated

solvent. Crystalline forms of COMPOUND 1 have improved bioavailability as compared to amporphous forms of COMPOUND 1. In particular, Form 3 is non-hygroscopic, and exhibits stability advantages (e.g., thermodynamic, chemical, or physical stability) at a relative humidity of up to 40%.

In one embodiment, at least a particular percentage by weight of COMPOUND 3 is crystalline. Particular weight percentages may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 10% and 100%. When a particular percentage by weight of COMPOUND 3 is crystalline, the remainder of COMPOUND 3 is the amorphous form of COMPOUND 3. Non-limiting examples of crystalline COMPOUND 3 include a single crystalline form of COMPOUND 3 or a mixture of different single crystalline forms. In some embodiments, COMPOUND 3 is at least 90% by weight crystalline. In some other embodiments, COMPOUND 3 is at least 95% by weight crystalline.

In another embodiment, a particular percentage by weight of the crystalline COMPOUND 3 is a specific single crystalline form or a combination of single crystalline forms. Particular weight percentages may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 10% and 100%. In another embodiment, COMPOUND 3 is at least 90% by weight of a single crystalline form. In another embodiment, COMPOUND 3 is at least 95% by weight of a single crystalline form.

In one embodiment, at least a particular percentage by weight of COMPOUND 1 is crystalline. Particular weight percentages may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 10% and 100%. When a particular percentage by weight of COMPOUND 1 is crystalline, the remainder of COMPOUND 1 is the amorphous form of COMPOUND 1. Non-limiting examples of crystalline COMPOUND 1 include a single crystalline form of COMPOUND 1 or a mixture of different single crystalline forms. In some embodiments, COMPOUND 1 is at least 90% by weight crystalline. In some other embodiments, COMPOUND 1 is at least 95% by weight crystalline.

In another embodiment, a particular percentage by weight of the crystalline COMPOUND 1 is a specific single crystalline form or a combination of single crystalline forms.

Particular weight percentages may be 10%, 20%, 30%, 40%, 50%, 60%, 70%, 75%, 80%, 85%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99%, 99.5%, 99.9%, or any percentage between 10% and 100%. In another embodiment, COMPOUND 1 is at least 90% by weight of a single crystalline form. In another embodiment, COMPOUND 1 is at least 95% by weight of a single crystalline form.

In the following description of COMPOUND 3, embodiments of the invention may be described with reference to a particular crystalline form of COMPOUND 3, as characterized by one or more properties as discussed herein. The descriptions characterizing the crystalline forms may also be used to describe the mixture of different crystalline forms that may be present in a crystalline COMPOUND 3. However, the particular crystalline forms of COMPOUND 3 may also be characterized by one or more of the characteristics of the crystalline form as described herein, with or without regard to referencing a particular crystalline form.

In the following description of COMPOUND 1, embodiments of the invention may be described with reference to a particular crystalline form of COMPOUND 1, as characterized by one or more properties as discussed herein. The descriptions characterizing the crystalline forms may also be used to describe the mixture of different crystalline forms that may be present in a crystalline COMPOUND 1. However, the particular crystalline forms of COMPOUND 1 may also be characterized by one or more of the characteristics of the crystalline form as described herein, with or without regard to referencing a particular crystalline form.

The crystalline forms are further illustrated by the detailed descriptions and illustrative examples given below. The XRPD peaks described in Tables 1 to 19 may vary by ± 0.2 depending upon the instrument used to obtain the data.

**Form 1**

In one embodiment, a single crystalline form, Form 1, of the COMPOUND 3 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 1, and data shown in Table 1, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 1, as shown in Table 1. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 1.

**Table 1**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.7 | 42.2 |
| 8.9 | 61.8 |
| 9.1 | 41.9 |
| 13.0 | 46.7 |
| 16.4 | 33.2 |
| 18.9 | 100.0 |
| 21.4 | 27.3 |
| 23.8 | 49.2 |
| 28.1 | 47.5 |

In another embodiment, Form 1 can be characterized by the peaks identified at 2θangles of 8.9, 13.0, 18.9, 23.8, and 28.1°. In another embodiment, Form 1 can be characterized by the peaks identified at 2θangles of 8.9, 18.9, and 24.8°.

**Form 2**

In one embodiment, a single crystalline form, Form 2, of the COMPOUND 3 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 2, and data shown in Table 2, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG.2, as shown in Table 2. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 2.

**Table 2**

| Angle 2-Theta° | Intensity % |
|---|---|
| 8.4 | 65.2 |
| 12.7 | 75.5 |
| 16.9 | 57.9 |
| 17.1 | 69.4 |
| 17.7 | 48.6 |
| 19.2 | 100.0 |
| 23.0 | 69.7 |
| 23.3 | 61.1 |
| 24.2 | 87.3 |

In another embodiment, Form 2 can be characterized by the peaks identified at 2θangles of 12.7, 17.1, 19.2, 23.0, and 24.2°. In another embodiment, Form 2 can be characterized by the peaks identified at 2θangles of 12.7, 19.2, and 24.2°.

In another embodiment, Form 2 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 3. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a strong endothermic transition with an onset temperature of about 88.2 °C with a melt at about 91.0 °C.

In another embodiment, Form 2 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 4. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 9.9 % of the weight of the sample as the temperature is changed from about 26.6°C to 150.0 °C.

**Form 3**

In one embodiment, a single crystalline form, Form 3, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 5, and data shown in Table 3, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 5, as shown in Table 3. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine or ten of the peaks shown in Table 3.

**Table 3**

| Angle 2-Theta° | Intensity % |
|---|---|
| 7.5 | 100.0 |
| 9.0 | 16.5 |
| 9.3 | 27.2 |
| 14.5 | 48.5 |
| 15.2 | 17.2 |
| 18.0 | 17.0 |

| | |
|---|---|
| 18.8 | 32.6 |
| 19.9 | 18.7 |
| 21.3 | 19.3 |
| 24.8 | 33.8 |

In another embodiment, Form 3 can be characterized by the peaks identified at 2θangles of 7.5, 9.3, 14.5, 18.8, 21.3, and 24.8°. In a further embodiment, Form 3 can be characterized by the peaks are identified at 2θangles of 7.5, 14.5, 18.8, and 24.8°. In another, embodiment, Form 3 can be characterized by the peaks identified at 2θangles of 7.5, 14.5, and 24.8°.

In another embodiment, Form 3 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 6. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a strong endothermic transition with an onset temperature of about 210.7 °C with a melt at about 213.4 °C.

In another embodiment, Form 3 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 7. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.03% of the weight of the sample as the temperature is changed from about 21°C to 196 °C and about 7.5% of the weight of the sample as the temperature is changed from about 196°C to 241°C.

In another embodiment, Form 3 is characterized by an X-ray powder diffraction pattern substantially similar to FIG. 5. In another embodiment, Form 3 is characterized by a differential scanning calorimetry (DSC) profile substantially similar to FIG. 6. In another embodiment, Form 3 is characterized by a thermal gravimetric analysis (TGA) profile substantially similar to FIG. 7. In further embodiments, a single crystalline form of Form 3 is characterized by one or more of the features listed in this paragraph. In another embodiment, Form 3 is characterized by a DVS profile substantially similar to FIG. 8.

**Form 4**

In one embodiment, a single crystalline form, Form 4, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 9, and data shown

in Table 4, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 9, as shown in Table 4. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 4.

**Table 4**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.2 | 28.9 |
| 6.5 | 38.0 |
| 7.5 | 29.5 |
| 18.6 | 25.0 |
| 19.0 | 34.8 |
| 19.4 | 58.8 |
| 19.9 | 100.0 |
| 22.9 | 31.0 |
| 24.7 | 36.9 |

In another embodiment, Form 4 can be characterized by the peaks identified at 2θangles of 6.5, 19.0, 19.4, 19.9, and 24.7°. In a further embodiment, Form 4 can be characterized by the peaks are identified at 2θangles of 6.5, 19.4, and 19.9°.

In another embodiment, Form 4 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 10. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a weak endothermic transition with an onset temperature of about 59.2 °C with a melt at about 85.5 °C and a strong endothermic transition with an onset temperature of about 205.2 °C with a melt at about 209.1 °C.

In another embodiment, Form 4 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 10. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 1.8 % of the weight of the sample as the temperature is changed from about 44.8 °C to 140.0 °C.

**Form 5**

In one embodiment, a single crystalline form, Form 5, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 11, and data shown in Table 5, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 11, as shown in Table 5. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 5.

**Table 5**

| Angle 2-Theta° | Intensity % |
|---|---|
| 7.1 | 100.0 |
| 14.5 | 40.0 |
| 17.1 | 29.8 |
| 19.2 | 6.1 |
| 21.8 | 47.8 |
| 22.7 | 7.7 |
| 23.4 | 6.5 |
| 28.5 | 2.1 |
| 29.4 | 17.6 |

In one embodiment, Form 5 can be characterized by the peaks identified at 2θangles of 7.1, 14.5, 17.1, and 21.8°. In a further embodiment, Form 5 can be characterized by the peaks are identified at 2θangles of 7.1 and 21.8°.

In another embodiment, Form 5 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 12. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a weak endothermic transition with an onset temperature of about 50.1 °C with a melt at about 77.5 °C and a strong endothermic transition with an onset temperature of about 203.1 °C with a melt at about 208.2 °C.

In another embodiment, Form 5 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 12. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.3 % of the weight of the sample as the temperature is changed from about 36.0 °C to 120.0 °C.

**Form 6**

In one embodiment, a single crystalline form, Form 6, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 13, and data shown in Table 6, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 13, as shown in Table 6. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 6.

**Table 6**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.3 | 53.7 |
| 7.2 | 100.0 |
| 8.1 | 71.5 |
| 12.2 | 19.2 |
| 12.7 | 34.0 |
| 14.9 | 37.2 |
| 17.9 | 21.4 |
| 18.4 | 31.0 |
| 26.4 | 20.2 |

In another embodiment, Form 6 can be characterized by the peaks identified at 2θangles of 6.3, 7.2, 8.1, 12.7, and 14.9°. In a further embodiment, Form 6 can be characterized by the peaks are identified at 2θangles of 6.3, 7.2, and 8.1°.

In another embodiment, Form 6 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 14. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by three weak endothermic transitions: with an onset temperature of about 61.7 °C with a melt at about 86.75 °C, an onset temperature of about 140.0 °C with a melt at about 149.0 °C, and an onset temperature of about 175.3 °C with a melt at about 192.1 °C.

In another embodiment, Form 6 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 14. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss

represents a loss of about 5.4 % of the weight of the sample as the temperature is changed from about 31.8 °C to 150.0 °C.

**Form 7**

In one embodiment, a single crystalline form, Form 7, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 15, and data shown in Table 7, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 15, as shown in Table 7. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 7.

**Table 7**

| Angle 2-Theta° | Intensity % |
|---|---|
| 9.7 | 32.5 |
| 14.1 | 59.0 |
| 18.6 | 35.7 |
| 19.1 | 100.0 |
| 20.2 | 50.6 |
| 21.8 | 65.9 |
| 23.5 | 72.4 |
| 25.7 | 57.7 |
| 28.9 | 27.7 |

In another embodiment, Form 7 can be characterized by the peaks identified at 2θangles of 14.1, 19.1, 21.8, 23.5, and 25.7°. In a further embodiment, Form 7 can be characterized by the peaks are identified at 2θangles of 19.1, 21.8, and 23.5°.

In another embodiment, Form 7 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 16. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is

characterized by a strong endothermic transition with an onset temperature of about 213.6 °C with a melt at about 214.7 °C.

In another embodiment, Form 7 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 16. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.01 % of the weight of the sample as the temperature is changed from about 32.2 °C to 150.0 °C.

**Form 8**

In one embodiment, a single crystalline form, Form 8, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 17, and data shown in Table 8, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 17, as shown in Table 8. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 8.

**Table 8**

| Angle 2-Theta° | Intensity % |
|---|---|
| 9.0 | 38.7 |
| 9.2 | 39.6 |
| 14.1 | 12.0 |
| 16.8 | 21.9 |
| 19.9 | 53.4 |
| 21.9 | 100.0 |
| 22.1 | 65.9 |
| 24.2 | 56.6 |
| 24.6 | 66.7 |

In another embodiment, Form 8 can be characterized by the peaks identified at 2θangles of 9.0, 9.2, 21.9, 22.1, 24.2, and 24.6°. In a further embodiment, Form 8 can be characterized by the peaks are identified at 2θangles of 21.9, 22.1, 24.2, and 24.6°.

In another embodiment, Form 8 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 18. The DSC graph plots the heat flow as a function of

temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a strong endothermic transition with an onset temperature of about 211.5 °C with a melt at about 212.8 °C.

In another embodiment, Form 8 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 18. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.2 % of the weight of the sample as the temperature is changed from about 31.2 °C to 150.0 °C.

**Form 9**

In one embodiment, a single crystalline form, Form 9, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 19, and data shown in Table 9, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 19, as shown in Table 9. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 9.

**Table 9**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.5 | 33.8 |
| 10.7 | 21.8 |
| 17.7 | 8.6 |
| 18.4 | 23.7 |
| 19.0 | 13.6 |
| 19.6 | 40.1 |
| 20.1 | 100.0 |
| 21.6 | 26.9 |
| 29.9 | 9.9 |

In another embodiment, Form 9 can be characterized by the peaks identified at 2θangles of 6.5, 19.6, 20.1, and 21.6°. In a further embodiment, Form 9 can be characterized by the peaks are identified at 2θangles of 19.6 and 20.1°.

In another embodiment, Form 9 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 20. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a strong endothermic transition with an onset temperature of about 172.3°C with a melt at about 175.95 °C and an endothermic transition with an onset temperature of about 192.3 °C with a melt at about 202.1 °C.

In another embodiment, Form 9 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 20. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.7 % of the weight of the sample as the temperature is changed from about 24.7 °C to 150.0 °C.

**Form 10**

In one embodiment, a single crystalline form, Form 10, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 21, and data shown in Table 10, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 21, as shown in Table 10. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 10.

**Table 10**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.7 | 46.8 |
| 7.7 | 31.0 |
| 9.1 | 100.0 |
| 10.8 | 76.9 |
| 13.3 | 11.6 |
| 16.0 | 15.6 |
| 19.9 | 84.6 |
| 21.9 | 52.3 |
| 25.8 | 15.2 |

In another embodiment, Form 10 can be characterized by the peaks identified at 2θangles of 6.7, 9.1, 10.8, 19.9, and 21.9°. In a further embodiment, Form 10 can be characterized by the peaks are identified at 2θangles of 9.1, 10.8, and 19.9°.

In another embodiment, Form 10 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 22. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by an endothermic transition with an onset temperature of about 139.9 °C with a melt at about 150.9 °C and an endothermic transition with an onset temperature of about 197.3 °C with a melt at about 201.3 °C.

In another embodiment, Form 10 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 22. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 0.5 % of the weight of the sample as the temperature is changed from about 31.0 °C to 120.0 °C.

**Form 11**

In one embodiment, a single crystalline form, Form 11, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 23, and data shown in Table 11, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 23, as shown in Table 11. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine or ten or eleven of the peaks shown in Table 11.

**Table 11**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.3 | 53.1 |
| 7.7 | 32.8 |
| 16.3 | 40.2 |
| 17.2 | 16.8 |
| 20.0 | 74.6 |
| 20.2 | 100.0 |
| 20.5 | 79.2 |

| | |
|---|---|
| 21.2 | 89.4 |
| 23.2 | 21.4 |
| 26.5 | 56.0 |
| 28.1 | 17.2 |

In another embodiment, Form 11 can be characterized by the peaks identified at 2θangles of 6.3, 20.0, 20.2, 20.5, 21.2, and 26.5°. In a further embodiment, Form 11 can be characterized by the peaks are identified at 2θangles of 20.0, 20.2, 20.5, and 21.2°.

In another embodiment, Form 11 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 24. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by an endothermic transition with an onset temperature of about 144.3 °C with a melt at about 154.5 °C and an endothermic transition with an onset temperature of about 193.4 °C with a melt at about 201.6 °C.

In another embodiment, Form 11 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 25. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 3.0 % of the weight of the sample as the temperature is changed from about 25.7 °C to 98.4 °C.

**Form 12**

In one embodiment, a single crystalline form, Form 12, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 26, and data shown in Table 12, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 26, as shown in Table 12. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 12.

**Table 12**

| **Angle 2-Theta°** | **Intensity %** |
|---|---|
| 7.2 | 75.7 |
| 7.4 | 100.0 |

| | |
|---|---|
| 8.0 | 61.3 |
| 8.2 | 52.4 |
| 13.2 | 9.4 |
| 16.5 | 27.2 |
| 18.6 | 32.7 |
| 20.2 | 23.6 |
| 20.8 | 18.7 |

In another embodiment, Form 12 can be characterized by the peaks identified at 2θangles of 7.2, 7.4, 8.0, 8.2, 16.5, and 18.6°. In a further embodiment, Form 12 can be characterized by the peaks are identified at 2θangles of 7.2, 7.4, 8.0, and 8.2°.

In another embodiment, Form 12 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 27. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by an endothermic transition with an onset temperature of about 80.9 °C with a melt at about 106.3 °C, an endothermic transition with an onset temperature of about 136.32 °C with a melt at about 150.3 °C, and a strong endothermic transition with an onset temperature of about 199.0 °C with a melt at about 203.1 °C.

In another embodiment, Form 12 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 27. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 6.4 % of the weight of the sample as the temperature is changed from about 25.9 °C to 80.0 °C, and a loss of about 7.2 % of the weight of the sample as the temperature is changed from about 25.9 °C to 150.0 °C.

**Form 13**

In one embodiment, a single crystalline form, Form 13, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 28, and data shown in Table 13, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 28, as shown in Table 13. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 13.

**Table 13**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.3 | 100.0 |
| 12.7 | 30.1 |
| 14.9 | 14.1 |
| 18.0 | 8.4 |
| 19.1 | 10.8 |
| 20.3 | 24.3 |
| 20.8 | 15.2 |
| 22.0 | 7.2 |
| 26.5 | 18.2 |

In another embodiment, Form 13 can be characterized by the peaks identified at 2θangles of 6.3, 12.7, 20.3, 20.8, and 26.5°. In a further embodiment, Form 13 can be characterized by the peaks are identified at 2θangles of 6.3, 12.7, and 20.3°.

In another embodiment, Form 13 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 29. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a weak endothermic transition with an onset temperature of about 144.1 °C with a melt at about 152.4 °C, and a strong endothermic transition with an onset temperature of about 198.1 °C with a melt at about 204.8 °C.

In another embodiment, Form 13 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 29. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 4.1 % of the weight of the sample as the temperature is changed from about 24.9 °C to 150.0 °C.

**Form 14**

In one embodiment, a single crystalline form, Form 14, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 30, and data shown in Table 14, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 30, as shown in Table 14. For

example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 14.

**Table 14**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.6 | 100.0 |
| 8.7 | 26.9 |
| 10.3 | 6.7 |
| 13.3 | 30.8 |
| 15.1 | 26.5 |
| 17.5 | 49.6 |
| 20.8 | 54.8 |
| 23.3 | 49.1 |
| 26.8 | 33.4 |

In another embodiment, Form 14 can be characterized by the peaks identified at 2θangles of 6.6, 17.5, 20.8 and 23.3°. In a further embodiment, Form 14 can be characterized by the peaks are identified at 2θangles of 6.6 and 20.8°.

In another embodiment, Form 14 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 31. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a weak endothermic transition with an onset temperature of about 122.3 °C with a melt at about 134.5 °C, and a strong endothermic transition with an onset temperature of about 207.6 °C with a melt at about 211.8 °C.

In another embodiment, Form 14 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 31. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 5.71 % of the weight of the sample as the temperature is changed from about 28.1 °C to 150.0 °C.

**Form 15**

In one embodiment, a single crystalline form, Form 15, of the COMPOUND 1 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 32, and data shown in Table 15, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 32, as shown in Table 15. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 15.

**Table 15**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.4 | 100.0 |
| 11.5 | 9.2 |
| 12.9 | 18.0 |
| 19.5 | 8.0 |
| 20.2 | 12.4 |
| 21.6 | 5.0 |
| 23.2 | 10.2 |
| 26.1 | 19.0 |
| 29.4 | 3.2 |

In another embodiment, Form 15 can be characterized by the peaks identified at 2θangles of 6.4, 12.9, 20.2, and 26.1°. In a further embodiment, Form 15 can be characterized by the peaks are identified at 2θangles of 6.4, 12.9, and 26.1°.

In another embodiment, Form 15 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 33. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a weak endothermic transition with an onset temperature of about 136.5 °C with a melt at about 140.1 °C, and a strong endothermic transition with an onset temperature of about 213.1 °C with a melt at about 215.2 °C.

In another embodiment, Form 15 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 33. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss represents a loss of about 7.6 % of the weight of the sample as the temperature is changed from about 28.7 °C to 150.0 °C.

**Form 16**

In one embodiment, a single crystalline form, Form 16, of the COMPOUND 3 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 34, and data shown in Table 16, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 34, as shown in Table 16. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 16.

**Table 16**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.8 | 35.5 |
| 10.1 | 30.7 |
| 10.6 | 53.1 |
| 13.6 | 46.0 |
| 14.2 | 63.8 |
| 17.2 | 26.4 |
| 18.4 | 34.0 |
| 19.2 | 100.0 |
| 23.5 | 3.8 |

In another embodiment, Form 16 can be characterized by the peaks identified at 2θangles of 6.8, 10.6, 13.6, 14.2, and 19.2°. In another embodiment, Form 16 can be characterized by the peaks identified at 2θangles of 10.6, 14.2, and 19.2°.

In another embodiment, Form 16 can be characterized by the differential scanning calorimetry profile (DSC) shown in FIG. 35. The DSC graph plots the heat flow as a function of temperature from a sample, the temperature rate change being about 10 °C /min. The profile is characterized by a strong endothermic transition with an onset temperature of about 169.7 °C with a melt at about 172.1 °C.

In another embodiment, Form 16 can be characterized by thermal gravimetric analysis (TGA) shown in FIG. 36. The TGA profile graphs the percent loss of weight of the sample as a function of temperature, the temperature rate change being about 10 °C /min. The weight loss

represents a loss of about 0.1 % of the weight of the sample as the temperature is changed from about 23.9 °C to 150.0 °C.

**Form 17**

In one embodiment, a single crystalline form, Form 17, of the COMPOUND 3 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 37, and data shown in Table 16, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 37, as shown in Table 17. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 17.

**Table 17**

| Angle 2-Theta° | Intensity % |
|---|---|
| 7.2 | 53.3 |
| 10.1 | 26.7 |
| 11.5 | 20.5 |
| 13.6 | 100.0 |
| 18.5 | 72.0 |
| 19.3 | 46.9 |
| 20.3 | 39.4 |
| 21.9 | 55.4 |
| 23.5 | 77.5 |

In another embodiment, Form 17 can be characterized by the peaks identified at 2θangles of 7.2, 13.6, 18.5, 19.3, 21.9, and 23.5°. In another embodiment, Form 16 can be characterized by the peaks identified at 2θangles of 13.6, 18.5, and 23.5°.

**Form 18**

In one embodiment, a single crystalline form, Form 18, of the COMPOUND 3 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 38, and data shown in Table 18, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 38, as shown in Table 18. For

example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight or nine of the peaks shown in Table 18.

**Table 18**

| Angle 2-Theta° | Intensity % |
|---|---|
| 6.4 | 45.4 |
| 8.4 | 84.0 |
| 9.8 | 100.0 |
| 16.1 | 26.0 |
| 16.9 | 22.7 |
| 17.8 | 43.6 |
| 19.7 | 40.4 |
| 21.1 | 20.5 |
| 26.1 | 15.9 |

In another embodiment, Form 18 can be characterized by the peaks identified at 2θangles of 6.4, 8.4, 9.8, 17.8, and 19.7°. In another embodiment, Form 18 can be characterized by the peaks identified at 2θangles of 8.4 and 9.8°.

**Form 19**

In one embodiment, a single crystalline form, Form 19, of the COMPOUND 3 is characterized by the X-ray powder diffraction (XRPD) pattern shown in FIG. 39, and data shown in Table 19, obtained using CuKa radiation. In a particular embodiment, the polymorph can be characterized by one or more of the peaks taken from FIG. 39, as shown in Table 19. For example, the polymorph can be characterized by one or two or three or four or five or six or seven or eight of the peaks shown in Table 19.

**Table 19**

| Angle 2-Theta° | Intensity % |
|---|---|
| 8.1 | 97.9 |
| 11.4 | 24.9 |
| 14.1 | 51.5 |
| 15.2 | 28.4 |
| 16.4 | 85.0 |
| 17.3 | 100.0 |
| 20.5 | 54.7 |
| 24.1 | 88.7 |

In another embodiment, Form 19 can be characterized by the peaks identified at 2θangles of 8.1, 14.1, 16.4, 17.3, 20.5, and 24.1°. In another embodiment, Form 19 can be characterized by the peaks identified at 2θangles of 8.1, 16.4, 17.3, and 24.1°.

Other embodiments are directed to a single crystalline form of COMPOUND 1 or COMPOUND 3 characterized by a combination of the aforementioned characteristics of any of the single crystalline forms discussed herein. The characterization may be by any combination of one or more of the XRPD, TGA, DSC, and DVS described for a particular polymorph. For example, the single crystalline form of COMPOUND 1 or COMPOUND 3 may be characterized by any combination of the XRPD results regarding the position of the major peaks in a XRPD scan; and/or any combination of one or more of parameters derived from data obtained from a XRPD scan. The single crystalline form of COMPOUND 1 or COMPOUND 3 may also be characterized by TGA determinations of the weight loss associated with a sample over a designated temperature range; and/or the temperature at which a particular weight loss transition begins. DSC determinations of the temperature associated with the maximum heat flow during a heat flow transition and/or the temperature at which a sample begins to undergo a heat flow transition may also characterize the crystalline form. Weight change in a sample and/or change in sorption/desorption of water per molecule of COMPOUND 1 or COMPOUND 3 as determined by water sorption/desorption measurements over a range of relative humidity (e.g., 0% to 90%) may also characterize a single crystalline form of COMPOUND 1 or COMPOUND 3.

The combinations of characterizations that are discussed above may be used to describe any of the polymorphs of COMPOUND 1 or COMPOUND 3 discussed herein, or any combination of these polymorphs.

## Pharmaceutical Compositions and Methods

### Compositions and routes of administration

The crystalline forms of COMPOUND 1 and COMPOUND 3 utilized in the methods described herein may be formulated together with a pharmaceutically acceptable carrier or adjuvant into pharmaceutically acceptable compositions prior to being administered to a subject.

The term "pharmaceutically acceptable carrier or adjuvant" refers to a carrier or adjuvant that may be administered to a subject, together with a compound, including a crystalline form thereof, and which does not destroy the pharmacological activity thereof and is nontoxic when administered in doses sufficient to deliver a therapeutic amount of the compound, including a crystalline form thereof.

In some embodiments, pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, self-emulsifying drug delivery systems (SEDDS) such as d-a-tocopherol polyethyleneglycol 1000 succinate, surfactants used in pharmaceutical dosage forms such as Tweens or other similar polymeric delivery matrices, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat. Cyclodextrins such as α-, β-, and γ-cyclodextrin, or chemically modified derivatives such as hydroxyalkylcyclodextrins, including 2- and 3-hydroxypropyl-β-cyclodextrins, or other solubilized derivatives may also be advantageously used to enhance delivery of compounds, including crystalline forms thereof, of the formulae described herein.

In some embodiments, the pharmaceutical compositions may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an

implanted reservoir, preferably by oral administration or administration by injection. The pharmaceutical compositions of one aspect of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. In some cases, the pH of the formulation may be adjusted with pharmaceutically acceptable acids, bases or buffers to enhance the stability of the formulated compound, including a crystalline form thereof, or its delivery form. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intraarticular, intraarterial, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

In some embodiments, the pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, or carboxymethyl cellulose or similar dispersing agents which are commonly used in the formulation of pharmaceutically acceptable dosage forms such as emulsions and or suspensions. Other commonly used surfactants such as Tweens or Spans and/or other similar emulsifying agents or bioavailability enhancers which are commonly used in the manufacture of pharmaceutically acceptable solid, liquid, or other dosage forms may also be used for the purposes of formulation.

In some embodiments, the pharmaceutical compositions may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, emulsions and aqueous suspensions, dispersions and solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents

include lactose and dried corn starch. When aqueous suspensions and/or emulsions are administered orally, the active ingredient may be suspended or dissolved in an oily phase is combined with emulsifying and/or suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

In some embodiments, the pharmaceutical compositions may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing crystalline forms of COMPOUND 1 or COMPOUND 3 with a suitable non-irritating excipient which is solid at room temperature but liquid at the rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

In some embodiments, topical administration of the pharmaceutical compositions is useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable ointment containing the active components suspended or dissolved in a carrier. Carriers for topical administration of crystalline forms of COMPOUND 1 or COMPOUND 3 include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxyethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound, including a crystalline form thereof, suspended or dissolved in a carrier with suitable emulsifying agents. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of one aspect of this invention may also be topically applied to the lower intestinal tract by rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in one aspect of this invention.

In some embodiments, the pharmaceutical compositions may be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The compounds, including crystalline forms thereof, described herein can, for example, be administered by injection, intravenously, intraarterially, subdermally, intraperitoneally, intramuscularly, or subcutaneously; or orally, buccally, nasally, transmucosally, topically, in an ophthalmic preparation, or by inhalation, with a dosage ranging from about 0.5 to about 100 mg/kg of body weight, alternatively dosages between 1 mg and 1000 mg/dose, every 4 to 120 hours, or according to the requirements of the particular drug. The methods herein contemplate administration of an effective amount of compound, including a crystalline form thereof, or compound composition to achieve the desired or stated effect. Typically, the pharmaceutical compositions of one aspect of this invention will be administered from about 1 to about 6 times per day or alternatively, as a continuous infusion. Such administration can be used as a chronic or acute therapy. The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. A typical preparation will contain from about 5% to about 95% active compound (w/w). Alternatively, such preparations contain from about 20% to about 80% active compound.

A subject may be administered a dose of COMPOUND 1 or COMPOUND 3 as described in Example 25. Lower or higher doses than those recited above may be required. Specific dosage and treatment regimens for any particular subject will depend upon a variety of factors, including the activity of the specific compound, including a crystalline form thereof, employed, the age, body weight, general health status, sex, diet, time of administration, rate of excretion, drug combination, the severity and course of the disease, condition or symptoms, the subject's disposition to the disease, condition or symptoms, and the judgment of the treating physician.

Upon improvement of a subject's condition, a maintenance dose of a compound, including a crystalline form thereof,, composition or combination of one aspect of this invention may be administered, if necessary. Subsequently, the dosage or frequency of administration, or both, may be reduced, as a function of the symptoms, to a level at which the improved condition is retained when the symptoms have been alleviated to the desired level. Subjects may, however, require intermittent treatment on a long-term basis upon any recurrence of disease symptoms.

Some embodiments of the invention are directed toward a tablet comprising at least one pharmaceutically acceptable carrier or diluent; and a crystalline form of COMPOUND 1 or COMPOUND 3. In other embodiments, the crystalline form of COMPOUND 1 or

COMPOUND 3 is at least 90% by weight a of a particular crystalline form; the particular crystalline form being a form described herein. In other embodiments, the crystalline form of COMPOUND 1 or COMPOUND 3 is at least 95% by weight a of a particular crystalline form; the particular crystalline form being a form described herein.

**Methods of Use**

The inhibitory activities of crystalline forms of COMPOUND 1 or COMPOUND 3 provided herein against IDH2 mutants (e.g., IDH2R140Q and IDH2R172K) can be tested by methods described in Example 12 of PCT Publication No. WO 2013/102431 and US Publication No. US 2013/0190287 hereby incorporated by reference in their entirety, or analogous methods.

Provided is a method for treating a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) comprising contacting a subject in need thereof with a crystalline form of COMPOUND 1 or COMPOUND 3. In one embodiment, the acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) to be treated is characterized by a mutant allele of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient. In one aspect of this embodiment, the mutant IDH2 has an R140X mutation. In another aspect of this embodiment, the R140X mutation is a R140Q mutation. In another aspect of this embodiment, the R140X mutation is a R140W mutation. In another aspect of this embodiment, the R140X mutation is a R140L mutation. In another aspect of this embodiment, the mutant IDH2 has an R172X mutation. In another aspect of this embodiment, the R172X mutation is a R172K mutation. In another aspect of this embodiment, the R172X mutation is a R172G mutation. A cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) can be analyzed by sequencing cell samples to determine the presence and specific nature of (e.g., the changed amino acid present at) a mutation at amino acid 140 and/or 172 of IDH2.

Also provided are methods of treating a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia

(CMML), or lymphoma (e.g., T-cell lymphoma) characterized by the presence of a mutant allele of IDH2 comprising the step of administering to subject in need thereof (a) a crystalline form of COMPOUND 1 or COMPOUND 3, or (b) a pharmaceutical composition comprising (a) and a pharmaceutically acceptable carrier.

Without being bound by theory, applicants believe that mutant alleles of IDH2 wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate, and in particular R140Q and/or R172K mutations of IDH2, characterize a subset of all types of cancers described herein, without regard to their cellular nature or location in the body. Thus, the compounds, including crystalline forms thereof, and methods of one aspect of this invention are useful to treat cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) that is characterized by the presence of a mutant allele of IDH2 imparting such activity and in particular an IDH2 R140Q and/or R172K mutation.

In one embodiment, the efficacy of treatment is monitored by measuring the levels of 2HG in the subject. Typically levels of 2HG are measured prior to treatment, wherein an elevated level is indicated for the use of a crystalline form of COMPOUND 1 or COMPOUND 3 to treat the cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma). Once the elevated levels are established, the level of 2HG is determined during the course of and/or following termination of treatment to establish efficacy. In certain embodiments, the level of 2HG is only determined during the course of and/or following termination of treatment. A reduction of 2HG levels during the course of treatment and following treatment is indicative of efficacy. Similarly, a determination that 2HG levels are not elevated during the course of or following treatment is also indicative of efficacy. Typically, the these 2HG measurements will be utilized together with other well-known determinations of efficacy of cancer treatment, such as reduction in number and size of tumors and/or other cancer-associated lesions, improvement in the general health of the subject, and alterations in other biomarkers that are associated with cancer treatment efficacy.

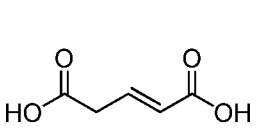
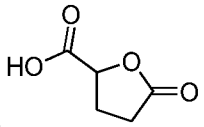
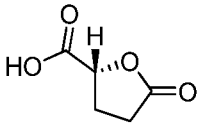
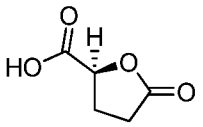
2HG can be detected in a sample by the methods of PCT Publication No. WO 2013/102431 and US Publication No. US 2013/0190287 hereby incorporated by reference in their entirety, or by analogous methods.

In one embodiment 2HG is directly evaluated.

In another embodiment a derivative of 2HG formed in process of performing the analytic method is evaluated. By way of example such a derivative can be a derivative formed in MS analysis. Derivatives can include a salt adduct, *e.g.,* a Na adduct, a hydration variant, or a hydration variant which is also a salt adduct, e.g., a Na adduct, e.g., as formed in MS analysis.

In another embodiment a metabolic derivative of 2HG is evaluated. Examples include species that build up or are elevated, or reduced, as a result of the presence of 2HG, such as glutarate or glutamate that will be correlated to 2HG, *e.g.,* R-2HG.

Exemplary 2HG derivatives include dehydrated derivatives such as the compounds provided below or a salt adduct thereof:


, 
, 
, and 
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In one embodiment the cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) is a tumor wherein at least 30, 40, 50, 60, 70, 80 or 90% of the tumor cells carry an IDH2 mutation, and in particular an IDH2 R140Q, R140W, or R140L and/or R172K or R172G mutation, at the time of diagnosis or treatment.

The pharmacological properties of crystalline forms of COMPOUND 1 or COMPOUND 3 are such that they are suitable for use in the treatment of a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) in a patient by administering to the patient a crystalline form of COMPOUND 1 or COMPOUND 3 in an amount effective to treat the cancer. In one embodiment, the cancer to be treated is AML. In some embodiments, the AML is relapsed and/or primary refractory. In other embodiments, the AML is untreated.

In another embodiment, the cancer to be treated is MDS with refractory anemia with excess blasts (subtype RAEB-1 or RAEB-2). In other embodiments, the MDS is untreated.

In another embodiment, the cancer to be treated is relapsed and/or primary refractory CMML.

Treatment methods described herein can additionally comprise various evaluation steps prior to and/or following treatment with a crystalline form of COMPOUND 1 or COMPOUND 3.

In one embodiment, prior to and/or after treatment with a crystalline form of COMPOUND 1 or COMPOUND 3, the method further comprises the step of evaluating the growth, size, weight, invasiveness, stage and/or other phenotype of the cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma).

In one embodiment, prior to and/or after treatment with a crystalline form of COMPOUND 1 or COMPOUND 3, the method further comprises the step of evaluating the IDH2 genotype of the cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma). This may be achieved by ordinary methods in the art, such as DNA sequencing, immuno analysis, and/or evaluation of the presence, distribution or level of 2HG.

In one embodiment, prior to and/or after treatment with a crystalline form of COMPOUND 1 or COMPOUND 3, the method further comprises the step of determining the 2HG level in the subject. This may be achieved by spectroscopic analysis, *e.g.,* magnetic resonance-based analysis, *e.g.,* MRI and/or MRS measurement, sample analysis of bodily fluid, such as blood, plasma, urine, or spinal cord fluid analysis, or by analysis of surgical material, *e.g.,* by mass-spectroscopy (e.g. LC-MS, GC-MS).

**Examples**

*Abbreviations*

ca approximately

$CHCl_3$ - chloroform

DCM - dichloromethane

DMF - dimethylformamide

$Et_2O$ - diethyl ether

EtOH - ethyl alcohol

EtOAc - ethyl acetate

MeOH - methyl alcohol

MeCN - acetonitrile

PE - petroleum ether

THF - tetrahydrofuran

AcOH - acetic acid

HCl - hydrochloric acid

$H_2SO_4$ - sulfuric acid

$NH_4Cl$ - ammonium chloride

KOH - potassium hydroxide

NaOH - sodium hydroxide

$Na_2CO_3$ - sodium carbonate

TFA - trifluoroacetic acid

$NaHCO_3$ - sodium bicarbonate

DMSO dimethylsulfoxide

DSC differential scanning calorimetry

DVS dynamic vapor sorption

GC gas chromatography

h hours

HPLC high performance liquid chromatography

min minutes

m/z mass to charge

MS mass spectrum

NMR nuclear magnetic resonance

RT room temperature

TGA thermal gravimetric analysis

XRPD X-ray powder diffraction / X-ray powder diffractogram / X-ray powder diffractometer

**General methods**

In the following examples, reagents were purchased from commercial sources (including Alfa, Acros, Sigma Aldrich, TCI and Shanghai Chemical Reagent Company), and used without

further purification. Nuclear magnetic resonance (NMR) spectra were obtained on a Brucker AMX-400 NMR (Brucker, Switzerland). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Mass spectra were run with electrospray ionization (ESI) from a Waters LCT TOF Mass Spectrometer (Waters, USA).

For exemplary compounds, including crystalline forms thereof, disclosed in this section, the specification of a stereoisomer (e.g., an (R) or (S) stereoisomer) indicates a preparation of that compound such that the compound is enriched at the specified stereocenter by at least about 90%, 95%, 96%, 97%, 98%, or 99%. The chemical name of each of the exemplary compound described below is generated by ChemDraw software.

**X-Ray Powder Diffraction (XRPD) parameters:** XRPD analysis was performed using a PANalytical Empyrean X-ray powder diffractometer (XRPD) with a 12-auto sample stage. The XRPD parameters used are listed in Table 20.

**Table 20.**

| | **Parameters for Reflection Mode** |
|---|---|
| X-Ray wavelength | Cu, kα,<br>Kα1 (Å): 1.540598, Kα2 (Å): 1.544426<br>Kα2/Kα1 intensity ratio: 0.50 |
| X-Ray tube setting | 45 kV, 40 mA |
| Divergence slit | Automatic |
| Scan mode | Continuous |
| Scan range (°2TH) | 3°-40° |
| Step size (°2TH) | 0.0170 |
| Scan speed (°/min) | About 10 |

For Form 3, XRPD analysis was performed using a LYNXEYE XE Detector (Bruker). The XRPD parameters used are listed in Table 21.

Table 21.

| | **Parameters for Reflection Mode** |
|---|---|
| X-Ray wavelength | Cu, kα,<br>Kα1 (Å): 1.54060, Kα2 (Å): 1.54439<br>Kα2/Kα1 intensity ratio: 0.50 |
| Scan range (°2TH) | 3°-40° |
| Step size (°2TH) | 0.012 |

**Differential Scanning Calorimetry (DSC) parameters:** DSC analysis was performed using a TA Q100, or Q200/Q2000 DSC from TA Instruments. The temperature was ramped from room temperature to the desired temperature at a heating rate of 10 °C/min using $N_2$ as the purge gas, with pan crimped.

**Thermogravimetric Analysis (TGA) parameters:** TGA analysis was performed using a TA Q500/Q5000 TGA from TA Instruments. The temperature was ramped from room temperature to the desired temperature at a heating rate of 10 °C/min or 20 °C/min using $N_2$ as the purge gas.

**Dynamic Vapor Sorption (DVS) parameters:** DVS was measured via a SMS (Surface Measurement Systems) DVS Intrinsic. The relative humidity at 25°C were calibrated against deliquescence point of LiCl, $Mg(NO_3)_2$ and KCl. The DVS Parameters used are listed in Table 22.

**Table 22**

| | DVS |
|---|---|
| Temperature | 25°C |
| Sample size | 10-20 mg |
| Gas and flow rate | $N_2$, 200 mL/min |
| dm/dt | 0.002%/min |
| Min. dm/dt stability duration | 10 min |
| Max. equilibrium time | 180 min |
| RH range | 60%RH-95%RH-0%RH-95%RH |
| RH step size | 10% (0%RH-90%RH, 90%RH--0%RH)<br>5% (90%RH-95%RH-90%RH) |

**Example 1: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3)**

***Example 1, Step 1: preparation of 6-trifluoromethyl-pyridine-2-carboxylic acid methyl ester***

To a solution of 6-trifluoromethyl-pyridine-2-carboxylic acid (300 g, 1.57 mol) in methanol (2.25 L) is added $SOCl_2$ (225 g, 1.88 mol) dropwise at room temperature, while maintaining room temperature. After addition, the mixture is heated to reflux and stirred for two hours then concentrated to remove the solvent. The crude product is diluted with ethyl acetate and washed with saturated $NaHCO_3$ solution. The organic layer is dried over anhydrous $Na_2SO_4$ and concentrated to give 6-trifluoromethyl- pyridine-2-carboxylic acid methyl ester, LCMS: m/z 206 $(M+H)^+$.

***Example 1, Step 2: preparation of 6-(6-Trifluoromethyl-pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione***

Sodium metal (13.46 g, 0.585 mol) is added to ethanol (1.35 L) and the mixture is stirred at room temperature until the sodium dissolves completely. To the resulting sodium ethoxide solution is added biuret (15.1 g, 0.146 mol) at 50°C and the solution is stirred at 50°C for 10 min, followed by addition of 6-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (90 g, 0.44 mol). The mixture is heated to reflux for 3 hours. The reaction mixture is concentrated and added to ice-water (1000 mL). Then concentrated HCl (24.3 mL, 0.29 mol) is added to

neutralize the mixture to a pH of between 7 and 8. The precipitated solid is collected by filtration and dried to give 6-(6-Trifluoromethyl -pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione, LCMS: m/z 259 $(M+H)^+$.

***Example 1, Step 3: preparation of 2, 4-Dichloro-6-(6-trifluoromethyl-pyridin-2-yl)-1, 3, 5-triazine***

To a solution of 6-(6-Trifluoromethyl-pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione (89 g, 0.345 mol) in $POCl_3$ (1335 mL) is added $PCl_5$ (286.6 g, 1.37 mol). The mixture is stirred at 100°C for 2 hours then concentrated. To the concentrate is added ethyl acetated (1.5 L), then the mixture is washed with water, followed by saturated $NaHCO_3$ solution. The organic layer is dried over anhydrous $Na_2SO_4$ and concentrated to give 2, 4-Dichloro-6-(6-tri-fluoromethyl-pyridin-2-yl)-1, 3, 5- triazine, LCMS: m/z 294.9 $(M+H)^+$.

***Example 1, Step 4: preparation of 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2-(trifluoro-methyl)- pyridin-4-yl)-1,3,5-triazin-2-amine***

To a solution of 2, 4-Dichloro-6-(6-trifluoromethyl-pyridin-2-yl)-1, 3, 5- triazine (200 g, 0.678 mol) in anhydrous THF (2 L) at room temperature, is added 2-(trifluoromethyl)pyridin-4-amine (131.8 g, 0.814 mol) and $NaHCO_3$ (85.68 g, 1.017 mol). The mixture is heated up to reflux and stirred for 18 hr. The reaction is concentrated to remove the volatiles and diluted in ethyl acetate, then washed with $H_2O$. The organic layer is dried over anhydrous $Na_2SO_4$ and concentrated. The product is recrystallized from dichloromethane as follows: the concentrate is dissolved in dichloromethane and the solvent is removed via rotary evaporator at low temperature (room temperature to 0°C), and the product precipitates from the solvent to give 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2- (trifluoro-methyl)-pyridin-4-yl)-1,3,5 -triazin-2-amine, LCMS: m/z 421.2 $(M+H)^+$.

***Example 1, Step 5: preparation of2-methyl-1-(4-(6-(trifluoromethyl)pyridin-2-yl)-6-(2-(trifluoromethyl)- pyridin-4-ylamino)-1,3,5-triazin-2-ylamino)propan-2-ol*** **(COMPOUND 3)**

To a solution of 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2-(trifluoro-methyl)-pyridin- 4-yl)-1,3,5-triazin-2-amine (201.2 g, 0.48 mmol) in THF (2 L), at room temperature, is added 1-amino-2-methylpropan-2-ol (51.3 g, 0.58 mol) and $NaHCO_3$ (60.5 g, 0.72 mol). The mixture is heated up to reflux for 16 to 24 hrs. The mixture is then concentrated to remove the volatiles and diluted in ethyl acetate, then washed with $H_2O$. The organic layer is dried over anhydrous $Na_2SO_4$ and concentrated. The concentrate is then dissolved in dichloromethane and

the solvent is removed via rotary evaporator at low temperature (room temperature to 0°C). The product is precipitated to afford 2-methyl-1-(4-(6-(trifluoromethyl)-pyridin-2-yl)-6-(2-(trifluoro-methyl)-pyridin-4-ylamino)-1,3,5-triazin- 2-ylamino)propan-2-ol, $^1$H NMR (METHANOL-$d_4$) δ 8.62-8.68 (m, 2 H), 8.47-8.50 (m, 1 H), 8.18-8.21 (m, 1 H), 7.96-7.98 (m, 1 H), 7.82-7.84 (m, 1 H), 3.56-3.63 (d, J = 28 Hz, 2 H), 1.30 (s, 6 H); LC-MS: m/z 474.3 $(M+H)^+$.

**Example 2: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3) Form 16**

***Example 2, Step 1: preparation of 6-trifluoromethyl-pyridine-2-carboxylic acid***

Diethyl ether (4.32 L) and hexanes (5.40 L) are added to the reaction vessel under $N_2$ atmosphere, and cooled to -75 °C to -65 °C. Dropwise addition of n-Butyl lithium (3.78 L in 1.6 M hexane) under $N_2$ atmosphere at below -65 °C is followed by dropwise addition of dimethyl amino ethanol (327.45 g, 3.67 mol) and after 10 min. dropwise addition of 2-trifluoromethyl pyridine (360 g, 2.45 mol). The reaction is stirred under $N_2$ while maintaining the temperature below -65 °C for about 2.0-2.5 hrs. The reaction mixture is poured over crushed dry ice under $N_2$, then brought to a temperature of 0 to 5 °C while stirring (approx. 1.0 to 1.5 h) followed by the addition of water (1.8 L). The reaction mixture is stirred for 5-10 mins and allowed to warm to 5-10 °C. 6N HCl (900 mL) is added dropwise until the mixture reached pH 1.0 to 2.0, then the mixture is stirred for 10-20 min. at 5-10 °C. The reaction mixture is diluted with ethyl acetate at 25-35 °C, then washed with brine solution. The reaction is concentrated and rinsed with n-heptane and then dried to yield 6-trifluoromethyl-pyridine-2-carboxylic acid.

***Example 2, Step 2: preparation of 6-trifluoromethyl-pyridine-2-carboxylic acid methyl ester***

Methanol is added to the reaction vessel under nitrogen atmosphere. 6-trifluoromethyl-pyridine-2-carboxylic acid (150 g, 0.785 mol) is added and dissolved at ambient temperature. Acetyl chloride (67.78 g, 0.863 mol) is added dropwise at a temperature below 45 °C. The reaction mixture is maintained at 65-70 °C for about 2-2.5 h, and then concentrated at 35-45 °C under vacuum and cooled to 25-35 °C. The mixture is diluted with ethyl acetate and rinsed with saturated $NaHCO_3$ solution then rinsed with brine solution. The mixture is concentrated at temp 35-45 $^0$C under vacuum and cooled to 25-35 °C, then rinsed with n-heptane and concentrated at

temp 35-45 °C under vacuum, then degassed to obtain brown solid, which is rinsed with n-heptane and stirred for 10-15 minute at 25-35 $^0$C. The suspension is cooled to -40 to -30 °C while stirring, and filtered and dried to provide 6-trifluoromethyl-pyridine-2-carboxylic acid methyl ester.

***Example 2, Step 3: preparation of 6-(6-Trifluoromethyl-pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione***

1 L absolute ethanol is charged to the reaction vessel under $N_2$ atmosphere and Sodium Metal (11.2 g, 0.488 mol) is added in portions under $N_2$ atmosphere at below 50 °C. The reaction is stirred for 5-10 minutes, then heated to 50-55 °C. Dried Biuret (12.5 g, 0.122 mol) is added to the reaction vessel under $N_2$ atmosphere at 50-55 °C temperature, and stirred 10-15 minutes. While maintaining 50-55 °C 6-trifluoromethyl-pyridine-2-carboxylic acid methyl ester (50.0 g, 0.244 mol) is added. The reaction mixture is heated to reflux (75-80 °C) and maintained for 1.5-2 hours. Then cooled to 35-40 °C, and concentrated at 45-50 °C under vacuum. Water is added and the mixture is concentrated under vacuum then cooled to 35-40 °C more water is added and the mixture cooled to 0 -5 $^0$C. pH is adjusted to 7-8 by slow addition of 6N HCl, and solid precipitated out and is centrifuged and rinsed with water and centrifuged again. The off white to light brown solid of 6-(6-Trifluoromethyl-pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione is dried under vacuum for 8 to 10 hrs at 50 °C to 60 °C under 600mm/Hg pressure to provide 6-(6-Trifluoromethyl-pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione.

***Example 2, Step 4: preparation of 2, 4-Dichloro-6-(6-trifluoromethyl-pyridin-2-yl)-1, 3, 5-triazine***

$POCl_3$ (175.0 mL) is charged into the reaction vessel at 20– 35 °C, and 6-(6-Trifluoromethyl-pyridin-2-yl)-1H-1,3,5-triazine-2,4-dione (35.0 g, 0.1355 mol) is added in portions at below 50 °C. The reaction mixture is de-gassed 5-20 minutes by purging with $N_2$ gas. Phosphorous pentachloride (112.86 g, 0.542 mol) is added while stirring at below 50 °C and the resulting slurry is heated to reflux (105-110 °C) and maintained for 3-4 h. The reaction mixture is cooled to 50-55 °C, and concentrated at below 55 °C then cooled to 20–30 °C. The reaction mixture is rinsed with ethyl acetate and the ethyl acetate layer is slowly added to cold water (temperature ~5 °C) while stirring and maintaining the temperature below 10 °C. The mixture is stirred 3-5 minutes at a temperature of between 10 to 20 °C and the ethyl acetate layer is

collected. The reaction mixture is rinsed with sodium bicarbonate solution and dried over anhydrous sodium sulphate. The material is dried 2-3 h under vacuum at below 45 °C to provide 2, 4-Dichloro-6-(6-trifluoromethyl-pyridin-2-yl)-1, 3, 5-triazine.

***Example 2, Step 5: preparation of 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2-(trifluoro-methyl)- pyridin-4-yl)-1,3,5-triazin-2-amine***

A mixture of THF (135 mL) and 2, 4-Dichloro-6-(6-trifluoromethyl-pyridin-2-yl)-1, 3, 5-triazine (27.0 g, 0.0915 mol) are added to the reaction vessel at 20 – 35 °C, then 4-amino-2-(trifluoromethyl)pyridine (16.31 g, 0.1006 mol) and sodium bicarbonate (11.52 g, 0.1372 mol) are added. The resulting slurry is heated to reflux (75-80 °C) for 20-24 h. The reaction is cooled to 30-40 °C and THF evaporated at below 45 °C under reduced pressure. The reaction mixture is cooled to 20–35 °C and rinsed with ethyl acetate and water, and the ethyl acetate layer collected and rinsed with 0.5 N HCl and brine solution. The organic layer is concentrated under vacuum at below 45 °C then rinsed with dichloromethane and hexanes, filtered and washed with hexanes and dried for 5-6h at 45-50 °C under vacuum to provide 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2-(trifluoro-methyl)- pyridin-4-yl)-1,3,5-triazin-2-amine.

***Example 2, Step 6: preparation of2-methyl-1-(4-(6-(trifluoromethyl)pyridin-2-yl)-6-(2-(trifluoromethyl)- pyridin-4-ylamino)-1,3,5-triazin-2-ylamino)propan-2-ol*** **COMPOUND 3**

THF (290 mL), 4-chloro-6-(6-(trifluoromethyl)pyridin-2-yl)-N-(2-(trifluoro-methyl)-pyridin-4-yl)-1,3,5-triazin-2-amine (29.0 g, 0.06893 mol), sodium bicarbonate (8.68 g, 0.1033 mol), and 1,1-dimethylaminoethanol (7.37 g, 0.08271 mol) are added to the reaction vessel at 20–35 °C. The resulting slurry is heated to reflux (75-80 °C) for 16-20 h. The reaction is cooled to 30-40 °C and THF evaporated at below 45 °C under reduced pressure. The reaction mixture is cooled to 20–35 °C and rinsed with ethyl acetate and water, and the ethyl acetate layer collected. The organic layer is concentrated under vacuum at below 45 °C then rinsed with dichloromethane and hexanes, filtered and washed with hexanes and dried for 8-10h at 45-50 °C under vacuum to provide 2-methyl-1-(4-(6-(trifluoromethyl)pyridin-2-yl)-6-(2-(trifluoromethyl)-pyridin-4-ylamino)-1,3,5-triazin-2-ylamino)propan-2-ol.

**Example 3: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 1**

**Method A:**

Slurry conversion is conducted by suspending ca 10 mg of Form 3 in 0.5-1.0 mL of water. After the suspension is stirred at 50°C for 48 h, the remaining solids are centrifuged to provide Form 1.

**Method B:**

9.61 mg of Form 3 is dissolved in 0.2 mL of ethanol. The solution is placed at ambient condition and ethanol is evaporated to get Form 1.

**Method C:**

6.93 mg of Form 3 is dissolved in 0.2 mL of isopropyl acetate. The solution is placed at ambient temprerature and isopropyl acetate is evaporated to get Form 1.

**Example 4: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 2**

**Method A:**

Slurry conversion is conducted by suspending ca 10 mg of Form 3 in 0.5-1.0 mL of water. After the suspension is stirred at RT for 48 h, the remaining solids are centrifuged to provide Form 2.

**Method B:**

6.07 mg of Form 3 is suspended in 1.0 mL of water. The suspension is stirred at room temperature for about 24 hours. The solid is isolated to obtain Form 2.

**Example 5: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1)**

Acetone (435.0 mL) and 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (87.0 g, 0.184 mol) are added to the reaction vessel at 20–35 °C. In a separate vessel, methanesulfonic acid is added over 10 minutes to cold (0-4 °C) acetone (191.4 mL) while stirring to prepare a methane sulfonic acid solution. While passing through a micron filter, the freshly prepared methanesulfonic acid solution is added dropwise to the reaction mixture. The resulting slurry is filtered using nutsche filter and washed with acetone. The filtered material is dried for 30-40 minutes using vacuum to

provide 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate.

**Example 6: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 3**

While stirring, acetone (961.1 ml) is added to reaction vessel. The reaction is agitated and cooled to 15 °C then methanesulfonic acid (28.3 g) is added and the reaction is aged for at least 10 minutes. Crystallization to Form 3 is accomplished via the following salt formation: 1) acetone (500 ml, 4.17 vol) is charged to the crystallizer, then the mixture is agitated (550 rpm) for 10 min., 2) COMPOUND 3 (120.0 g, 253.5 mmol) is charged into crystallizer *via* solid charger over 45 min., 3) the solid charger is rinsed with acetone (100 ml, 0.83 vol), 4) the reaction is stirred (550 rpm) and heated to 35 °C to obtain a clear solution (in 10 min), 5) a first portion (2%) of MSA/acetone solution (0.3 mol/L,18.1 ml,3.8 ml/min) is added over 5 min *via* a piston pump, then the pump pipeline is washed with acetone (5 ml, 0.04 vol), 6) the mixture is aged at 35 °C for 10 to15 min, while ensuring the solution remains clear, 7) COMPOUND 1 seed (2.4 g as generated in Example 5, 2 wt%) is added, to the clear solution, 8) a second portion (49%) of MSA/acetone solution (0.3 mom/L, 444 ml, 3.7 ml/min) is added over 2 hrs, 9) the mixture is aged at 35 °C for 30 min, 10) a third portion (49%) of MSA/acetone solution (0.3 mom/L, 444 ml, 7.4 ml/min) is added over 1 hr, 11) the mixture is aged at 35 °C for 2 hr, 12) the mixture is cooled to 20 °C for 1 hr, 13) the mixture is filtered and the cake washed with acetone (240 ml twice), 17) and dried under vacuum at 30 °C; to provide Form 3 crystals.

**Example 7: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 4**

Reactive crystallization is conducted by mixing 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (0.1 mol/L) and methanesulfonic acid (0.1 mol/L) in MeCN to provide Form 4.

**Example 8: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 5**

Reactive crystallization is conducted by mixing 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (0.1 mol/L) and methanesulfonic acid (0.1 mol/L) in isopropyl alcohol to provide Form 5.

**Example 9: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 6**

Slow evaporation is performed by dissolving ca 10 mg of Form 3 in 0.4-3.0 mL of solvent in a 3-mL glass vial. The vials are covered with foil with about 6 to 8 holes and the visually clear solutions are subjected to slow evaporation at RT to induce precipitation. Then the solids are isolated. Form 6 is provided when the solvent or solvent mixture is MeOH, EtOH, IPA, THF, MeOH/Toluene=3:1, MeOH/CAN=3:1, MeOH/IPAc=3:1, MeOH/$H_2O$=3:1, EtOH/Acetone=5:1, EtOH/DCM=5:1, MeOH/Dioxane=3:1, MeOH/MTBE=3:1, EtOH/Acetone=1:1, and THF/$H_2O$=3:1.

**Example 10: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 7**

Reactive crystallization is conducted by quickly adding methanesulfonic acid (0.1 mol/L) to 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (0.1 mol/L) in acetone or MeCN to provide Form 7.

**Example 11: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 8**

**Method A**

Methanesulfonic acid (0.1 mol/L) is quickly added to 2-Methyl-1-[(4-[6-

(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (0.1 mol/L) in acetone to provide Form 8.

**Method B**

Form 12 is heated to 155°C in TGA and cooled to RT to provide Form 8.

**Example 12: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 9**

2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (0.1 mol/L) and methanesulfonic acid (0.1 mol/L) is mixed in acetone, and Form 9 immediately precipitates out of solution.

**Example 13: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 10**

Form 10 is produced by either heating Form 12 to 80°C at 10°C/min or keeping Form 12 under $N_2$ sweeping condition for 1 h in TGA.

**Example 14: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 11**

Form 11 is obtained by heating Form 6 to 80 °C or heating Form 13 to 100°C in the XRPD.

**Example 15: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 12**

**Method A**

Slow cooling is conducted by dissolving ca10 mg of Form 3 in 0.3-1.0 mL solvent or solvent mixture at 60 °C. Suspensions are filtered at 60 °C and the filtrate is collected. The saturated solution is cooled from 60 °C to 5 °C in an incubator at a rate of 0.05 °C /min. If no

precipitation is observed, the solution is subjected to evaporation at RT to induce precipitation. The solids are isolated to provide Form 12 when the solvent or solvent mixture is MeOH/$H_2O$=3:1, n-PrOH/$H_2O$=3:1, or THF/MTBE=3:1.

**Method B**

Solution vapor diffusion is conducted in solvents at RT by dissolving ca 10 mg of Form 3 in MeOH to obtain a clear solution in a 3-mL vial. The vial is sealed into a 20-mL vial filled with ca 3 mL water, and kept at RT for 5 to 7 days, allowing sufficient time to precipitate. The solids are separated to provide Form 12.

**Example 16: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 13**

**Method A:**

Form 13 is obtained by heating Form 6 to 80 °C and cooling to RT.

**Method B:**

Slurry conversion is conducted starting from mixtures of Form 6 and Form 12 at water activity of 0.31 at RT.

**Example 17: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 14**

Solution vapor diffusion is conducted in solvents at RT by dissolving ca 10 mg of Form 3 in MeOH to obtain a clear solution in a 3-mL vial. The vial is sealed into a 20-mL vial filled with ca 3 mL heptane, and kept at RT for 5 to 7 days, allowing sufficient time to precipitate. The solids are separated to provide Form 14.

**Example 18: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate Form 15**

Solution vapor diffusion is conducted in solvents at RT by dissolving ca 10 mg of Form 3 in EtOH to obtain a clear solution in a 3-mL vial. The vial is sealed into a 20-mL vial filled with

ca 3 mL IPAc or MTBE, and kept at RT for 5 to 7 days, allowing sufficient time to precipitate. The solids are separated to provide Form 15.

**Example 20: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 17**

**Method A:**

10.26 mg of Form 16 is suspended in 0.4 mL heptane. The suspension is stirred at RT for about 24 hours. The solid is isolated to obtain Form 17.

**Method B:**

10.10 mg of Form 16 is suspended in 0.2 mL methyl tert-butyl ether. The suspension is stirred at RT for about 24 hours. The solid is isolated to obtain Form 17.

**Example 21: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 18**

8.17 mg of Form 16 is dissolved in 0.2 mL MeOH. The solution is kept at ambient RT and MeOH is evaporated to provide Form 18.

**Example 22: Synthesis of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol Form 19**

905.61 mg of Form 16 is suspended in 5.0 mL of water. The suspension is stirred at RT for about 4 hours, and the solid is isolated to provide Form 19.

In Examples 23, 24, and 25 below, COMPOUND 1 may be amorphous, or a mixture of crystalline forms, or a single crystalline form.

**Example 23: *In vitro* experiments**

*2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate reduces intracellular and extracellular levels of 2-HG in a dose-dependent manner*

TF-1/IDH2 (R140Q) mutant cells are treated *in vitro* for 7 days with vehicle (dimethylsulfoxide; DMSO) or increasing levels of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol

methanesulfonate (at concentrations of 1.6 to 5000 nM). The intracellular levels of 2-HG are reduced in the mutant cell line (from 15.5 mM with DMSO to 0.08 mM with 5 μM 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate) and the reduction is concentration-dependent. With this dose titration, the intracellular $IC_{50}$ for 2-HG inhibition is calculated as 16 nM and the inhibitory concentration, 90% ($IC_{90}$) is 160 nM.

*2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate reduces vimentin levels associated with elevated levels of 2-HG, indicating a reduction in immature (undifferentiated) cell lines*

Following 7 days of treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate, vimentin expression, a stem cell marker, induced by IDH2 (R140Q) in TF-1 cells is reduced to baseline levels at 2-HG levels below 1 mM (i.e., 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate dose >200 nM).

The functional consequence of inhibiting IDH2 and thereby reducing intracellular 2-HG levels also is evaluated in the TF-1 IDH2 (R140Q) mutant cell model.

*2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate reduces IDH2 (R140Q)-induced GM-CSF-independent growth in TF-1 cells*

Upon treatment of TF-1 IDH2 (R140Q) cells with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (1 μM) for 7 days, 2-HG production is inhibited by >99% and GM-CSF independent growth conferred by the expression of TF-1 IDH2 (R140Q) is reversed.

*2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate reduces histone hypermethylation associated with elevated levels of 2-HG*

Following treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate, histone hypermethylation induced by IDH2 (R140Q) in TF-1 cells is reversed based on Western

blot analysis. A concentration-dependent reduction in histone methylation is observed at all 4 histone marks (H3K4me3, H3K9me3, H3K27me3, and H3K36me3). This effect is most apparent at 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate concentrations known to reduce intracellular 2-HG levels below 1 mM (i.e., 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate dose >200 nM) in the TF-1 IDH2 (R140Q) mutant cell system). The $IC_{50}$ for histone demethylation at H3K4me3 following 7 days of treatment is calculated as 236 nM. This result is consistent with the requirement to dose at >$IC_{90}$ for 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate in order to alter histone hypermethylation and is consistent with the 200 nM dose of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate needed to induce changes in histone methylation within the first 7 days.

*2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate reverses the differentiation block induced by the IDH2 (R140Q) mutation in TF-1 erythroleukemia cell lines*

Treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate restores the EPO-induced expression of both hemoglobin gamma 1/2 and Kruppel-like factor 1(KLF-1), a transcription factor that regulates erythropoiesis, in TF-1 IDH2 (R140Q) mutant cells when the 2-HG levels fall below 1 mM.

*Treatment of primary human AML blast cells with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate leads to an increase in cellular differentiation*

IDH2 (R140Q) mutant patient samples are treated in an *ex vivo* assay with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate. Living cells are sorted and cultured in the presence or absence of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (500, 1000, and 5000 nM). Cells are counted at Days 3, 6, 9, and 13 and normalized to DMSO control. Upon compound

treatment, a proliferative burst is seen starting at Day 6 consistent with the onset of cellular differentiation. Following 9 days of treatment *ex vivo*, the bone marrow blasts are analyzed for morphology and differentiation status in the presence or absence of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate; the cytologic analysis is blinded with regard to treatment. Cytology reveals that the percentage of blast cells decreases from 90% to 55% by Day 6 and is further reduced to 40% by Day 9 of treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate. Furthermore, there is a clear increase in the population of more differentiated cells as noted by an increase in metamyelocytes.

In summary, *ex vivo* treatment of primary human IDH2 (R140Q) mutant AML cells with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate results in a decrease in intracellular 2-HG and differentiation of the AML blasts through the macrophage and granulocytic lineages. These data demonstrate that inhibition of mutant IDH2 is able to relieve a block in differentiation present in this leukemic subset.

**Example 24: *In vivo* experiments**

*In vivo treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate in a mouse xenograft model led to a reduction in tumor 2-HG concentrations*

Pharmacokinetic/pharmacodynamic (PK/PD) studies are conducted in female nude mice inoculated subcutaneously with U87MG IDH2 (R140Q) tumor. Animals receive vehicle or single or multiple oral doses of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate at doses ranging from 10 to 150 mg/kg.

Tumor 2-HG concentration decreases rapidly following a single oral dose of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate. Tumor 2-HG concentration increases when the plasma concentration of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate

decreases below 1000 ng/mL.

In this model, tumor 2-HG levels decrease to baseline, as found in wild-type tissue, following 3 consecutive 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate doses of 25 mg/kg or above (twice daily, 12 hour dosing interval). The estimated area under the 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate concentration × time curve from 0 to 12 hours ($AUC_{0\text{-}12hr}$) that results in sustained 90% tumor 2-HG inhibition ($EAUC_{90[0\text{-}12hr]}$) and sustained 97% tumor 2-HG inhibition ($EAUC_{97[0\text{-}12h]}$) are approximately 5000 and 15200 hr•ng/mL, respectively.

*Effect of treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate or cytarabine on survival, tumor burden, and tumor differentiation in tumor bearing mice and naïve mice*

40 NOD/SCID mice are engrafted on Day 1 with $2*10^6$/mouse of AMM7577-P2 (HuKemia® model, Crown BioScience Inc.) frozen cells that may be thawed out from liquid $N_2$. Peripheral blood samples are collected weekly for FACS analysis of human leukemia cells starting at Week 3 post-cell inoculation. Plasma and urine samples are collected weekly starting at Week 3 until the termination point. When the tumor growth is about 10% of human CD45+ cell in peripheral blood samples, the engrafted mice may be randomly allocated into 5 groups using the treatment schedule denoted in Table 23.

**Table 23.**

| Group# | Treatment | n | Route | Treatment schedule | Survival at study termination |
|---|---|---|---|---|---|
| **1** | Vehicle | 9 | PO/BID 8/16 interval | Day 48-84 | 0/9 |
| **2** | COMPOUND 1, 5mg/kg | 9 | PO/BID 8/16 interval | Day 48-84 | 4/9 |
| **3** | COMPOUND 1 15mg/kg | 9 | PO/BID 8/16 | Day 48-84 | 6/9 |

| | | | | | |
|---|---|---|---|---|---|
| | | | interval | | |
| **4** | COMPOUND 1, 45mg/kg | 9 | PO/BID 8/16 interval | Day 48-84 | 9/9 |
| **5** | cytarabine, 2mg/kg | 4 | 5 Days | Day 48-52 | 0/4 |
| **6** | Age-matched naïve | 5 | - | No treatment | 5/5 |

As shown in Table 23, treatment with 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1) in a mutant positive AML mouse model, resulted in a dose dependent survival advantage in comparison to cytarabine. In the group of mice receiving the highest dose of COMPOUND 1 (Group 4, 45 mg/kg) all 9 mice survived until the study was completed. A dose dependent decrease in leukemia and evidence of normal differentiation was seen in all COMPOUND 1 treated animals.

**Example 25:**

The clinical study is a Phase 1, multicenter, open-label, dose-escalation, safety, PK/PD, and clinical activity evaluation of orally administered 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1) in subjects with advanced hematologic malignancies that harbor an IDH2 mutation. Primary study objectives include 1) assessment of the safety and tolerability of treatment with COMPOUND 1 administered continuously as a single agent dosed orally twice daily (approximately every 12 hours) on Days 1 to 28 of a 28-day cycle in subjects with advanced hematologic malignancies, and 2) determination of the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose of COMPOUND 1 in subjects with advanced hematologic malignancies. Secondary study objectives include 1) description of the dose-limiting toxicities (DLTs) of COMPOUND 1 in subjects with advanced hematologic malignancies, 2) characterization of the pharmacokinetics (PK) of COMPOUND 1 and its metabolite 6-(6-(trifluoromethyl)pyridin-2-yl)-N2-(2-(trifluoromethyl)pyridin-4-yl)-1,3,5-triazine-2,4-diamine (COMPOUND 2) in subjects with advanced hematologic malignancies, 3) characterization of the PK/pharmacodynamic (PD)

relationship of COMPOUND 1 and 2-hydroxygluturate (2-HG), and 4) characterization of the clinical activity associated with COMPOUND 1 in subjects with advanced hematologic malignancies.

Exploratory study objectives include 1) characterization of the PD effects of COMPOUND 1 in subjects with advanced hematologic malignancies by the assessment of changes in the patterns of cellular differentiation of isocitrate dehydrogenase-2 (IDH2)-mutated tumor cells and changes in histone and deoxyribonucleic acid (DNA) methylation in IDH2-mutated tumor cells, and 2) evaluation of gene mutation status, global gene expression profiles, and other potential prognostic markers (cytogenetics) in IDH2-mutated tumor cells, as well as subclonal populations of non-IDH2 mutated tumor cells, to explore predictors of anti-tumor activity and/or resistance, and 3) evaluation of changes in the metabolic profiles in IDH2-mutated tumor cells.

The study includes a dose escalation phase to determine MTD followed by expansion cohorts to further evaluate the safety and tolerability of the MTD. The dose escalation phase will utilize a standard "3 + 3" design. During the dose escalation phase, consented eligible subjects will be enrolled into sequential cohorts of increasing doses of COMPOUND 1. Each dose cohort will enroll a minimum of 3 subjects.

Toxicity severity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03. A DLT is defined as follows. Non-hematologic includes all clinically significant non-hematologic toxicities CTCAE ≥Grade 3. (For example, alopecia is not considered a clinically significant event). Hematologic includes prolonged myelosuppression, defined as persistence of ≥3 Grade neutropenia or thrombocytopenia (by NCI CTCAE, version 4.03, leukemia-specific criteria, i.e., marrow cellularity <5% on Day 28 or later from the start of study drug without evidence of leukemia) at least 42 days after the initiation of Cycle 1 therapy. Leukemia-specific grading should be used for cytopenias (based on percentage decrease from baseline: 50 to 75% = Grade 3, >75% = Grade 4).Due to frequent co-morbidities and concurrent medications in the population under study, attribution of adverse events (AEs) to a particular drug is challenging. Therefore, all AEs that cannot clearly be determined to be unrelated to COMPOUND 1 will be considered relevant to determining DLTs.

Increases in the dose of COMPOUND 1 for each dose cohort will be guided by an accelerated titration design, where the dose will be doubled (100% increase) from one cohort to the next until COMPOUND 1-related NCI CTCAE Grade 2 or greater toxicity is observed in any subject within the cohort. The MTD is the highest dose that causes DLTs in <2 of 6 subjects.

If no DLTs are identified during the dose escalation phase, dose escalation may continue for 2 dose levels above the projected maximum biologically effective dose, as determined by an ongoing assessment of PK/PD and any observed clinical activity, to determine the recommended Phase 2 dose.

Following determination of the recommended Phase 2 dose, 3 expansion cohorts (in specific hematologic malignancy indications) of approximately 12 subjects each will be treated at that dose. The purpose of the expansion cohorts is to evaluate and confirm the safety and tolerability of the recommended Phase 2 dose in specific disease indications. Subjects enrolled in these cohorts will undergo the same procedures as subjects in the dose escalation cohorts with the exception that they will not be required to undergo the Day -3 through Day 1 PK/PD assessments.

Subjects will undergo screening procedures within 28 days prior to the start of study drug treatment to determine eligibility. Screening procedures include medical, surgical, and medication history, confirmation of IDH2 mutation in leukemic blasts (if not documented previously), physical examination, vital signs, Eastern Cooperative Oncology Group (ECOG) performance status (PS), 12-lead electrocardiogram (ECG), evaluation of left ventricular ejection fraction (LVEF), clinical laboratory assessments (hematology, chemistry, coagulation, urinalysis, and serum pregnancy test), bone marrow biopsy and aspirate, and blood and urine samples for 2-HG measurement.

Three days prior to starting the twice daily dosing of COMPOUND 1 (Day -3), the first 3 subjects enrolled in each cohort in the dose escalation phase will receive a single dose of COMPOUND 1 in clinic and have serial blood and urine samples obtained for determination of blood and urine concentrations of COMPOUND 1, its metabolite, and 2-HG. A full 72-hour PK/PD profile will be conducted: subjects will be required to remain at the study site for 10 hours on Day -3 and return on Days -2, -1, and 1 for 24, 48, and 72 hour samples, respectively. During the in-clinic period on Day -3, clinical observation and serial 12-lead ECGs and vital signs assessments will be conducted.

Twice daily treatment with COMPOUND 1 will begin on C1D1; for subjects who did not undergo the Day -3 PK/PD assessments, clinical observation and serial 12-lead ECGs and vital signs assessments will be conducted over 8 hours following their first dose of COMPOUND 1 on C1D1. Safety assessments conducted during the treatment period include physical examination, vital signs, ECOG PS, 12-lead ECGs, evaluation of LVEF, and clinical laboratory assessments (hematology, chemistry, coagulation, and urinalysis).

All subjects will undergo PK/PD assessments over a 10-hour period on both C1D15 and C2D1. In addition, subjects will collect urine samples at home once every other week (starting on C1D8) prior to the morning dose for determination of 2-HG levels.

Subjects will have the extent of their disease assessed, including bone marrow aspirates and biopsies and peripheral blood, at screening, on Day 15, Day 29 and Day 57, and every 56 days thereafter while on study drug treatment, independent of dose delays and/or dose interruptions, and/or at any time when progression of disease is suspected. Response to treatment will be determined by the Investigators based on modified International Working Group (IWG) response criteria for acute myelogenous leukemia (AML).

Subjects may continue treatment with COMPOUND 1 until disease progression, occurrence of a DLT, or development of other unacceptable toxicity. All subjects are to undergo an end of treatment assessment (within approximately 5 days of the last dose of study drug); in addition, a follow-up assessment is to be scheduled 28 days after the last dose.

A patient must meet all of the following inclusion criteria to be enrolled in the clinical study. 1) Subject must be ≥18 years of age; 2) Subjects must have advanced hematologic malignancy including: a) Relapsed and/or primary refractory AML as defined by World Health Organization (WHO) criteria, b) untreated AML, ≥60 years of age and are not candidates for standard therapy due to age, performance status, and/or adverse risk factors, according to the treating physician and with approval of the Medical Monitor, c) Myelodysplastic syndrome with refractory anemia with excess blasts (subtype RAEB-1 or RAEB-2), or considered high-risk by the Revised International Prognostic Scoring System (IPSS-R) (Greenberg et al. *Blood.* 2012;120(12):2454-65) that is recurrent or refractory, or the patient is intolerant to established therapy known to provide clinical benefit for their condition (i.e., patients must not be candidates for regimens known to provide clinical benefit), according to the treating physician and with approval of the Medical Monitor, and d) Subjects with other relapsed and/or primary refractory

hematologic cancers, for example CMML, who fulfill the inclusion/excluding criteria may be considered on a case-by case basis; 3) subjects must have documented IDH2 gene-mutated disease based on local evaluation. Analysis of leukemic blast cells for IDH2 gene mutation is to be evaluated at screening; 4) Subjects must be amenable to serial bone marrow biopsies, peripheral blood sampling, and urine sampling during the study; 5) Subjects or their legal representatives must be able to understand and sign an informed consent; 6) Subjects must have ECOG PS of 0 to 2; 7) Platelet count ≥20,000/μL (Transfusions to achieve this level are allowed.) Subjects with a baseline platelet count of <20,000/μL due to underlying malignancy are eligible with Medical Monitor approval; 8) Subjects must have adequate hepatic function as evidenced by: a) Serum total bilirubin ≤1.5 × upper limit of normal (ULN), unless considered due to Gilbert's disease or leukemic organ involvement, and b) Aspartate aminotransferase, ALT, and alkaline phosphatase (ALP) ≤3.0 × ULN, unless considered due to leukemic organ involvement; 9) Subjects must have adequate renal function as evidenced by a serum creatinine ≤2.0 × ULN; 10) Subjects must be recovered from any clinically relevant toxic effects of any prior surgery, radiotherapy, or other therapy intended for the treatment of cancer. (Subjects with residual Grade 1 toxicity, for example Grade 1 peripheral neuropathy or residual alopecia, are allowed with approval of the Medical Monitor.); and 11) Female subjects with reproductive potential must have a negative serum pregnancy test within 7 days prior to the start of therapy. Subjects with reproductive potential are defined as one who is biologically capable of becoming pregnant. Women of childbearing potential as well as fertile men and their partners must agree to abstain from sexual intercourse or to use an effective form of contraception during the study and for 90 days (females and males) following the last dose of COMPOUND 1.

COMPOUND 1 will be provided as 5, 10, 50, and 200 mg free-base equivalent strength tablets to be administered orally.

The first 3 subjects in each cohort in the dose escalation portion of the study will receive a single dose of study drug on Day -3; their next dose of study drug will be administered on C1D1 at which time subjects will start dosing twice daily (approximately every 12 hours) on Days 1 to 28 in 28-day cycles. Starting with C1D1, dosing is continuous; there are no inter-cycle rest periods. Subjects who are not required to undergo the Day -3 PK/PD assessments will initiate twice daily dosing (approximately every 12 hours) with COMPOUND 1 on C1D1.

Subjects are required to fast (water is allowed) for 2 hours prior to study drug administration and for 1 hour following study drug administration.

The dose of COMPOUND 1 administered to a subject will be dependent upon which dose cohort is open for enrollment when the subject qualifies for the study. The starting dose of COMPOUND 1 to be administered to the first cohort of subjects is 30 mg (free-base equivalent strength) administered orally twice a day.

Subjects may continue treatment with COMPOUND 1 until disease progression, occurrence of a DLT, or development of other unacceptable toxicity.

**Criteria for evaluation**

Safety:

AEs, including determination of DLTs, serious adverse events (SAEs), and AEs leading to discontinuation; safety laboratory parameters; physical examination findings; vital signs; 12-lead ECGs; LVEF; and ECOG PS will be monitored during the clinical study. The severity of AEs will be assessed by the NCI CTCAE, Version 4.03.

Pharmacokinetics and pharmacodynamics:

Serial blood samples will be evaluated for determination of concentration-time profiles of COMPOUND 1 and its metabolite COMPOUND 2. Urine samples will be evaluated for determination of urinary excretion of COMPOUND 1 and its metabolite COMPOUND 2. Blood, bone marrow, and urine samples will be evaluated for determination of 2-HG levels.

Pharmacokinetic assessments:

Serial blood samples will be drawn before and after dosing with COMPOUND 1 in order to determine circulating plasma concentrations of COMPOUND 1 (and, if technically feasible, the metabolite COMPOUND 2). The blood samples will also be used for the determination of 2-HG concentrations.

For the first 3 subjects enrolled in a cohort during the dose escalation phase, a single dose of COMPOUND 1 will be administered on Day -3 (i.e., 3 days prior to their scheduled C1D1 dose). Blood samples will be drawn prior to the single-dose administration of COMPOUND 1 and at the following time points after administration: 30 minutes and 1, 2, 3, 4, 6, 8, 10, 24, 48,

and 72 hours. After 72 hours of blood sample collection, subjects will begin oral twice daily dosing of COMPOUND 1 (i.e., C1D1). The PK/PD profile from Day -3 through Day 1 is optional for additional subjects enrolled in the dose escalation phase (i.e., for any subjects beyond the 3 initial subjects enrolled in a cohort) and is not required for subjects enrolled in the expansion cohorts.

All subjects will undergo 10-hour PK/PD sampling on C1D15 and C2D1 (i.e., on Days 15 and 29 of twice daily dosing). For this profile, one blood sample will be drawn immediately prior to that day's first dose of COMPOUND 1 (i.e., dosing with COMPOUND 1 will occur at the clinical site); subsequent blood samples will be drawn at the following time points after dosing: 30 minutes, and 1, 2, 3, 4, 6, 8, and 10 hours. Additionally, one blood sample will be drawn at the End of Treatment Visit.

The timing of blood samples drawn for COMPOUND 1 concentration determination may be changed if the emerging data indicates that an alteration in the sampling scheme is needed to better characterize COMPOUND 1's PK profile.

For the first 3 subjects enrolled in a cohort during the dose escalation phase, urine will be collected on Day -3 prior to and over the first 72 hours following a single dose of COMPOUND 1 to provide a preliminary estimate of the extent to which COMPOUND 1 (and, if technically feasible, metabolite COMPOUND 2) is eliminated unchanged in the urine. Samples also will be analyzed for 2-HG concentrations and for urinary creatinine concentration.

Five urine collections will be obtained during this 72-hour period. An initial urine collection will be made prior to COMPOUND 1 dosing (at least 20 mL). The 2nd urine collection will be obtained over approximately 10 hours following COMPOUND 1 administration, and a subsequent 8-hour urine collection will be obtained between discharge from the clinic and the return visit on the following day (for the 24-hour blood draw). The 4th and 5th urine collections will be obtained at approximately the 48-hour and 72-hour blood draws. Additionally, a urine collection (at least 20 mL) will occur at the End of Treatment Visit. Urine sampling from Day -3 through Day 1 is optional for additional subjects enrolled in the dose escalation phase (i.e., for any subjects beyond the 3 initial subjects enrolled in a cohort) and is not required for subjects enrolled in the expansion cohorts.

The volume of each collection will be measured and recorded and sent to a central laboratory for determination of the urinary COMPOUND 1 concentration.

Pharmacodynamic assessments:

Serial blood samples will be drawn before and after dosing with COMPOUND 1 in order to determine circulating concentrations of 2-HG. Samples collected for PK assessments also will be used to assess 2-HG levels. In addition, subjects will have blood drawn for determination of 2-HG levels at the screening assessment.

The timing of blood samples drawn for 2-HG concentration determination may be changed if the emerging data indicate that an alteration in the sampling scheme is needed to better characterize the 2-HG response to COMPOUND 1 treatment.

Bone marrow also will be assessed for 2-HG levels.

Urine will be collected before and after dosing with COMPOUND 1 for the determination of concentrations of 2-HG. Samples collected for PK assessments on Day -3 will also be used to assess 2-HG levels. In addition, subjects will have urine sample collected for determination of 2-HG levels at the screening assessment and the End of Treatment visit.

In addition, after initiating twice daily COMPOUND 1 treatment, all subjects will collect urine samples at home once every two weeks (starting on C1D8) prior to the morning dose. At least 20 mL of urine will be collected for each sample. Subjects will be instructed on how to store the urine and to bring all samples collected to the clinic at the next visit.

The volume of each collection will be measured and recorded and sent to a central laboratory for determination of urinary 2-HG concentration. An aliquot from each collection will be analyzed for urinary creatinine concentration.

Clinical activity:

Serial blood and bone marrow sampling will be evaluated during the clinical study to determine response to treatment based on modified IWG response criteria in AML. The clinical activity of COMPOUND 1 will be evaluated by assessing response to treatment according to the 2006 modified IWG criteria for MDS, MDS/myeloproliferative neoplasms (MPN) or AML (Cheson BD, et al. *J Clin Oncol.* 2003;21(24):4642-9, Cheson BD, et al. *Blood.* 2006;108(2):419-25).

Disease response to treatment will be assessed through the evaluation of bone marrow aspirates and biopsies, along with complete blood counts and examination of peripheral blood

films. Subjects will have the extent of their disease assessed and recorded at screening, on Days 15, 29, and 57, every 56 days thereafter while on study drug treatment, independent of dose-delays and/or dose interruptions, and/or at any time when progression of disease is suspected. An assessment also will be conducted at the End of Treatment visit for subjects who discontinue the study due to reasons other than disease progression.

Bone marrow aspirates and biopsies are to be obtained at screening, Day 15, Day 29, Day 57, every 56 days thereafter independent of dose delays and/or interruptions, at any time when progression of disease is suspected, and at the End of Treatment visit. Bone marrow aspirates and core sampling should be performed according to standard of care and analyzed at the local site's laboratory in accordance with the International Council for Standardization in Hematology (ICSH) Guidelines (Lee SH, et al. *Int J Lab Hematol.* 2008;30(5):349-64). Bone marrow core biopsies and aspirate are to be evaluated for morphology, flow cytometry, and for karyotype to assess potential clinical activity. Aliquots of the bone marrow and/or peripheral blood blast cells also will be evaluated at central laboratories for 2-HG levels, gene expression profiles, histone and DNA methylation patterns, and metabolomic profiling. Peripheral blood for the evaluation of leukemic blast cells is to be obtained at screening, Day15, Day 29, Day 57, every 56 days thereafter independent of dose delays and/or interruptions, at any time when progression of disease is suspected, and at the End of Treatment visit. Cell counts and flow cytometry will be used to assess the state of differentiation of blast cells collected from bone marrow and peripheral blood. Side scatter also will be analyzed to determine the complexity of the blast cells in response to COMPOUND 1.

**Statistical analysis**

Statistical analyses will be primarily descriptive in nature since the goal of the study is to determine the MTD of COMPOUND 1. Tabulations will be produced for appropriate disposition, demographic, baseline, safety, PK, PD, and clinical activity parameters and will be presented by dose level and overall. Categorical variables will be summarized by frequency distributions (number and percentages of subjects) and continuous variables will be summarized by descriptive statistics (mean, standard deviation, median, minimum, and maximum).
Adverse events will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Separate tabulations will be produced for all treatment-

emergent AEs (TEAEs), treatment-related AEs (those considered by the Investigator as at least possibly drug related), SAEs, discontinuations due to AEs, and AEs of at least Grade 3 severity. By-subject listings will be provided for deaths, SAEs, DLTs, and AEs leading to discontinuation of treatment.

Descriptive statistics will be provided for clinical laboratory, ECG interval, LVEF, and vital signs data, presented as both actual values and changes from baseline relative to each on-study evaluation and to the last evaluation on study. Shift analyses will be conducted for laboratory parameters and ECOG PS.

Descriptive statistics will be used to summarize PK parameters for each dose group and, where appropriate, for the entire population. The potential relationship between plasma levels of COMPOUND 1 and blood, plasma or urine 2-HG levels will be explored with descriptive and graphical methods.

Response to treatment as assessed by the site Investigators using modified IWG will be tabulated. Two-sided 90% confidence intervals on the response rates will be calculated for each dose level and overall. Data will also be summarized by type of malignancy for subjects in the cohort expansion phase.

While the foregoing invention has been described in some detail for purposes of clarity and understanding, these particular embodiments are to be considered as illustrative and not restrictive. It will be appreciated by one skilled in the art from a reading of this disclosure that various changes in form and detail can be made without departing from the true scope of the invention, which is to be defined by the appended claims rather than by the specific embodiments.

The patent and scientific literature referred to herein establishes knowledge that is available to those with skill in the art. Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. The issued patents, applications, and references that are cited herein are hereby incorporated by reference to the same extent as if each was specifically and individually indicated to be incorporated by reference. In the case of inconsistencies, the present disclosure, including definitions, will control.

## Claims

1. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3), wherein the isolated crystalline form is Form 16, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 6.8, 10.6, 13.6, 14.2, and 19.2°.

2. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3), wherein the isolated crystalline form is Form 1, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 8.9, 13.0, 18.9, 23.8, and 28.1°.

3. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol (COMPOUND 3), wherein the isolated crystalline form is Form 2, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 12.7, 17.1, 19.2, 23.0, and 24.2°.

4. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1), wherein the isolated crystalline form is Form 3, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 7.5, 9.3, 14.5, 18.8, 21.3, and 24.8°.

5. The isolated crystalline form of claim 4, characterized by an X-ray powder diffraction pattern substantially similar to FIGURE 5.

6. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1), wherein the isolated crystalline form is Form 7, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 14.1, 19.1, 21.8, 23.5, and 25.7°.

6. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1), wherein the isolated crystalline form is Form 8, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 9.0, 9.2, 21.9, 22.1, 24.2, and 24.6°.

7. An isolated crystalline form of 2-Methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate (COMPOUND 1), wherein the isolated crystalline form is Form 9, characterized by an X-ray powder diffraction pattern having peaks at 2θangles of 6.5, 19.6, 20.1, and 21.6°.

8. A method of treating a cancer selected from acute myelogenous leukemia (AML), myelodysplastic syndrome (MDS), chronic myelomonocytic leukemia (CMML), or lymphoma (e.g., T-cell lymphoma) characterized by the presence of an IDH2 mutation, wherein the IDH2 mutation results in a new ability of the enzyme to catalyze the NAPH-dependent reduction of α-ketoglutarate to *R*(-)-2-hydroxyglutarate in a patient, comprising the step of administering to the patient in need thereof a crystalline form of any one of claims 1 to 7.

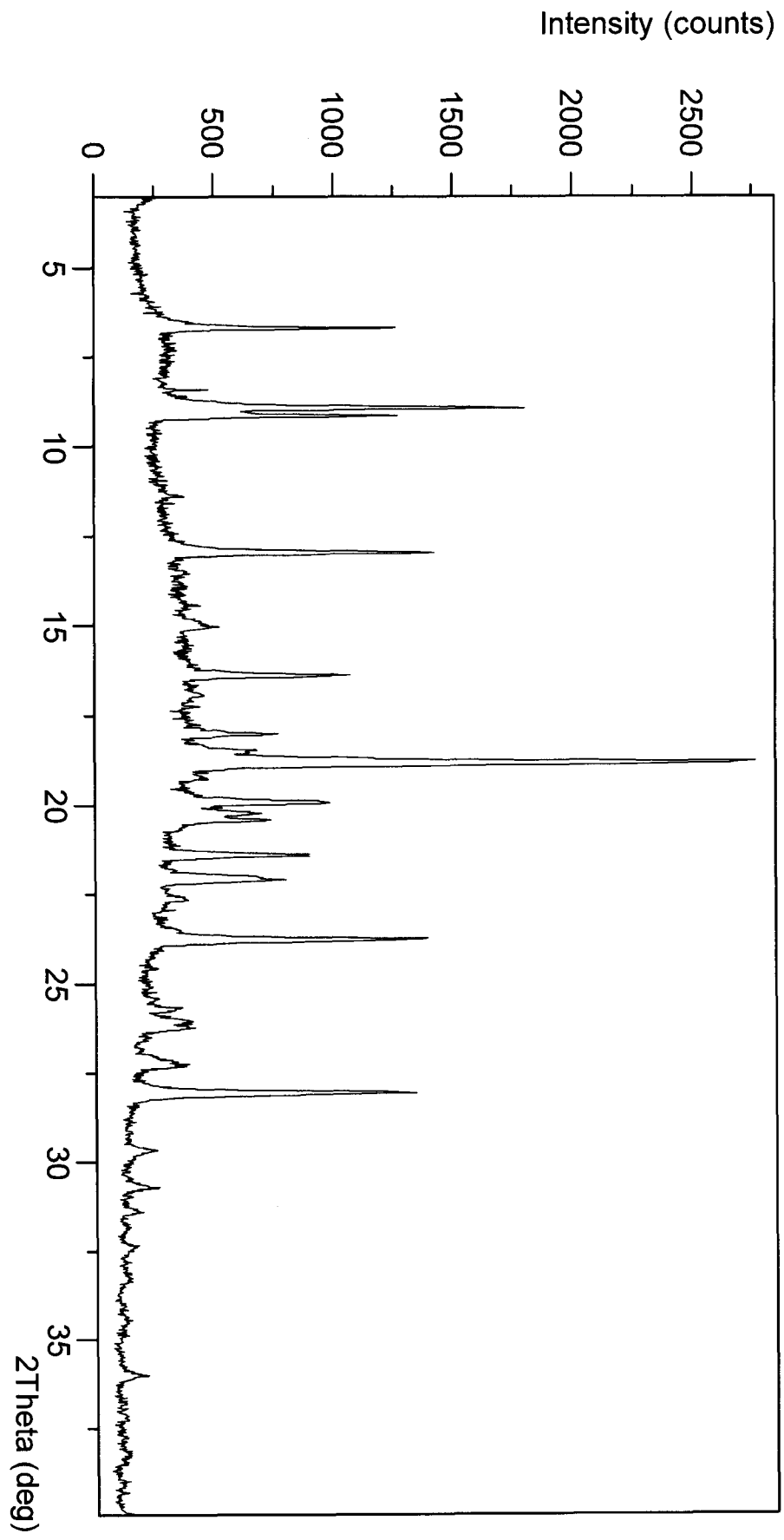


FIGURE 1. XRPD pattern of Form 1

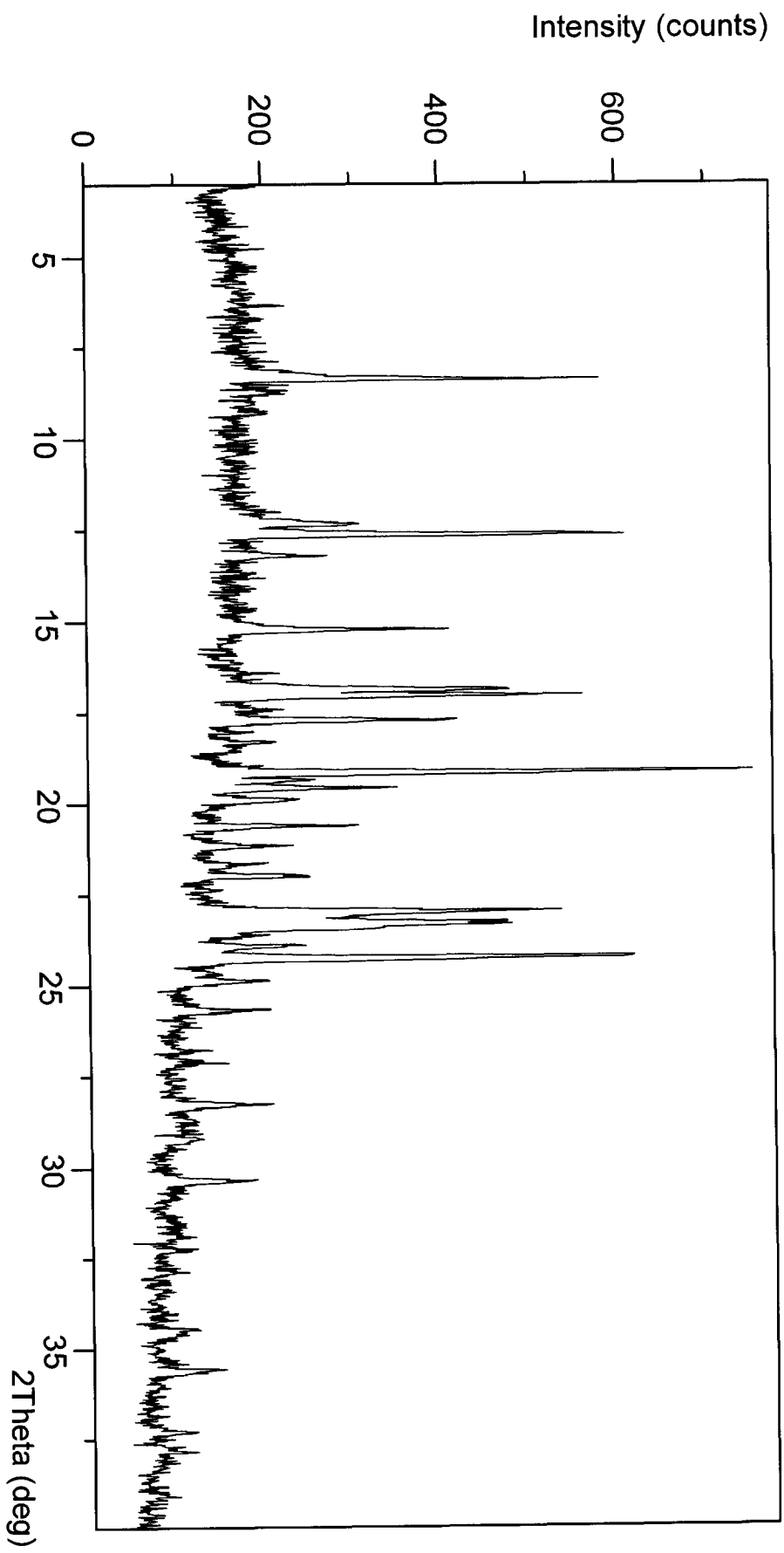


FIGURE 2. XRPD pattern of Form 2

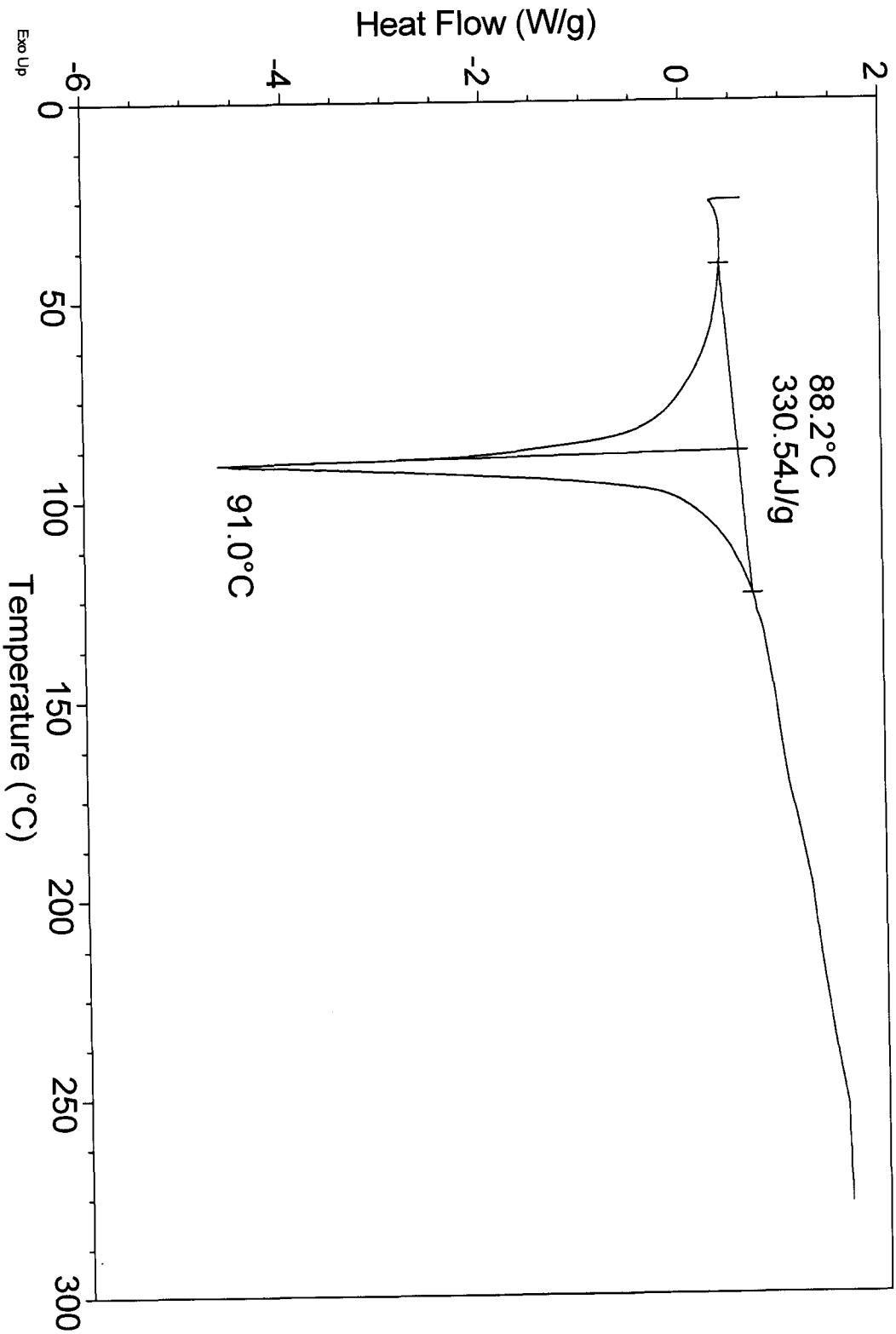


FIGURE 3. DSC profile of Form 2

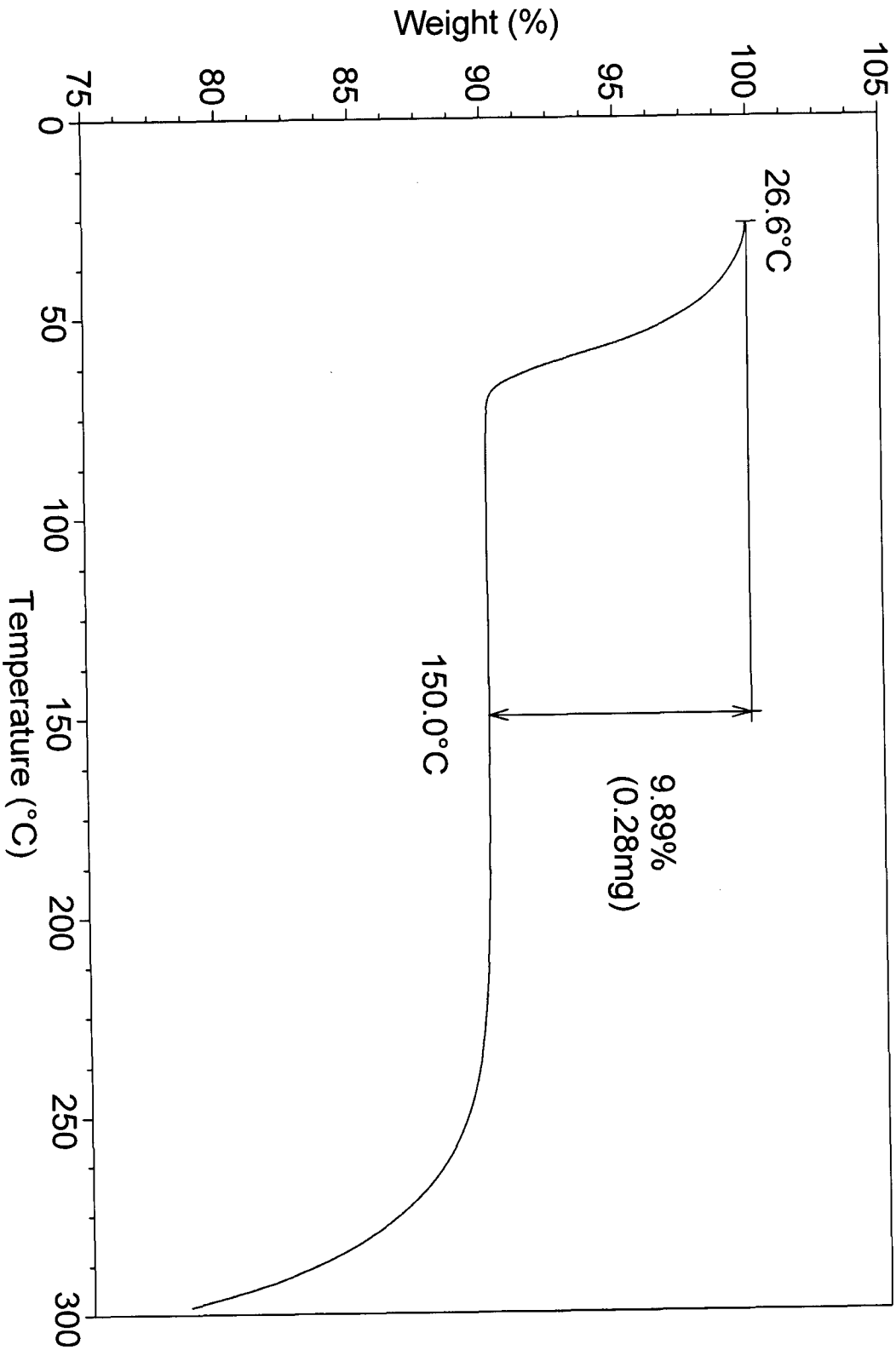


FIGURE 4. TGA profile of Form 2

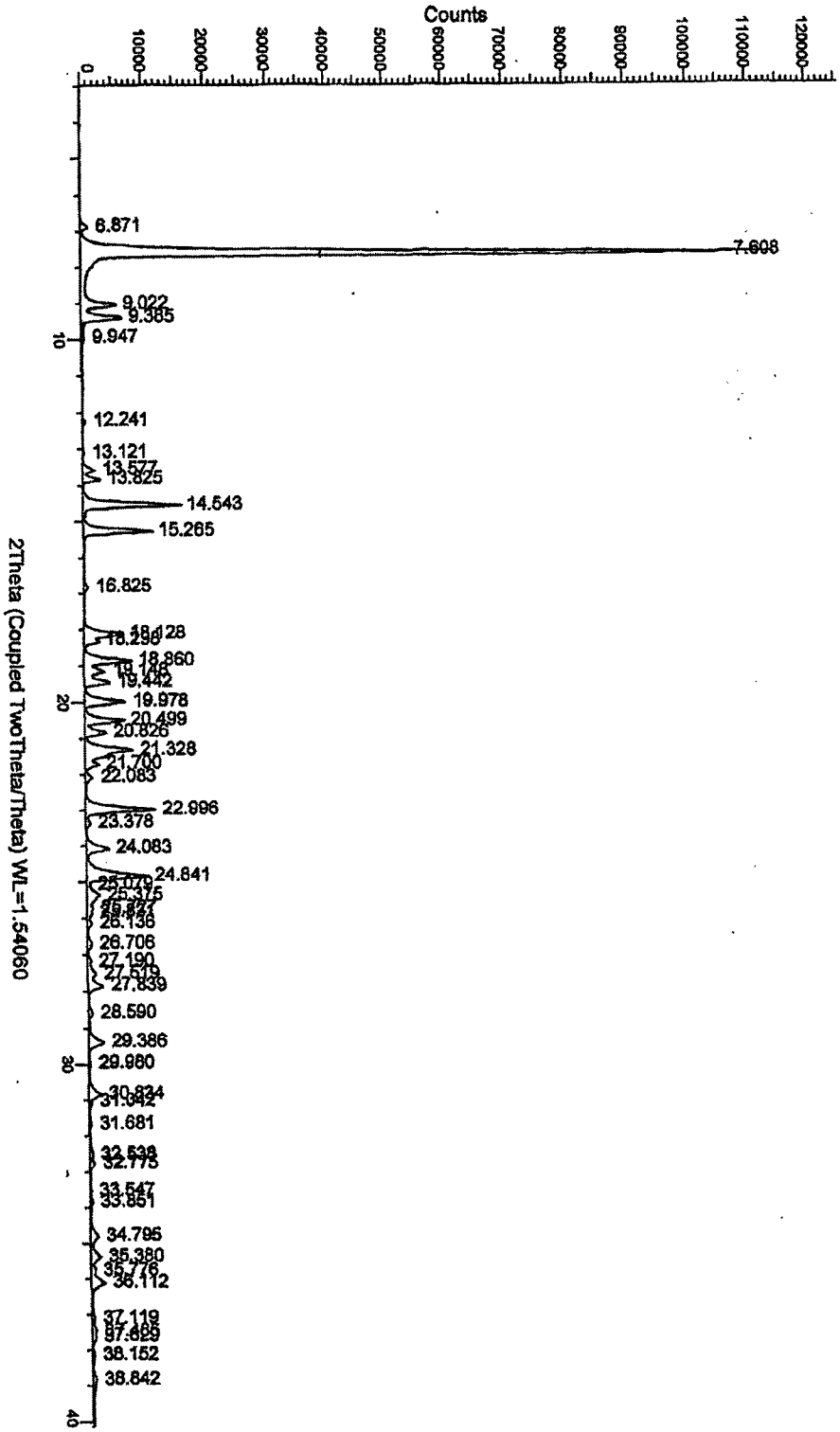


FIGURE 5. XRPD pattern of Form 3

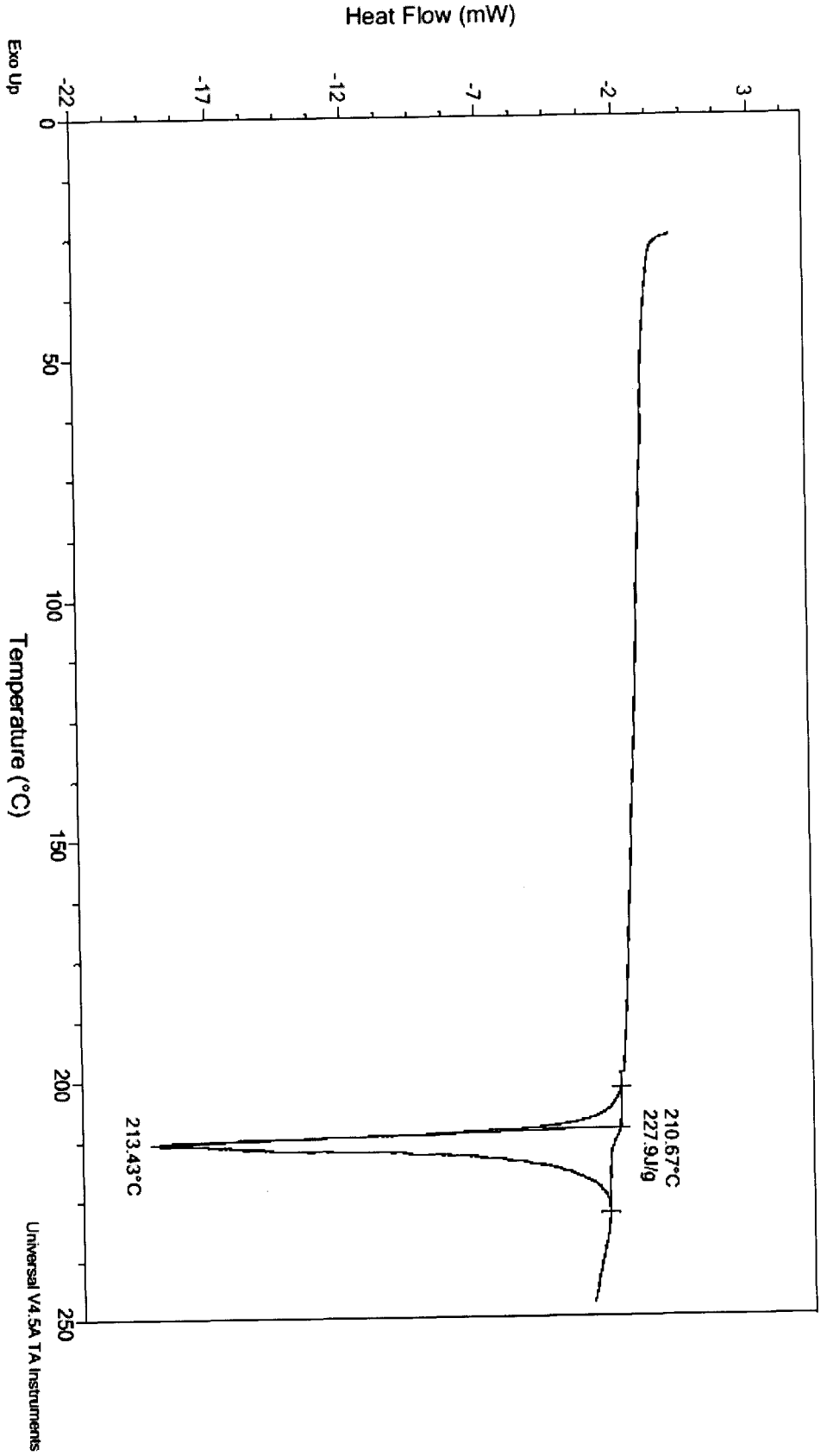


FIGURE 6. DSC profile of Form 3

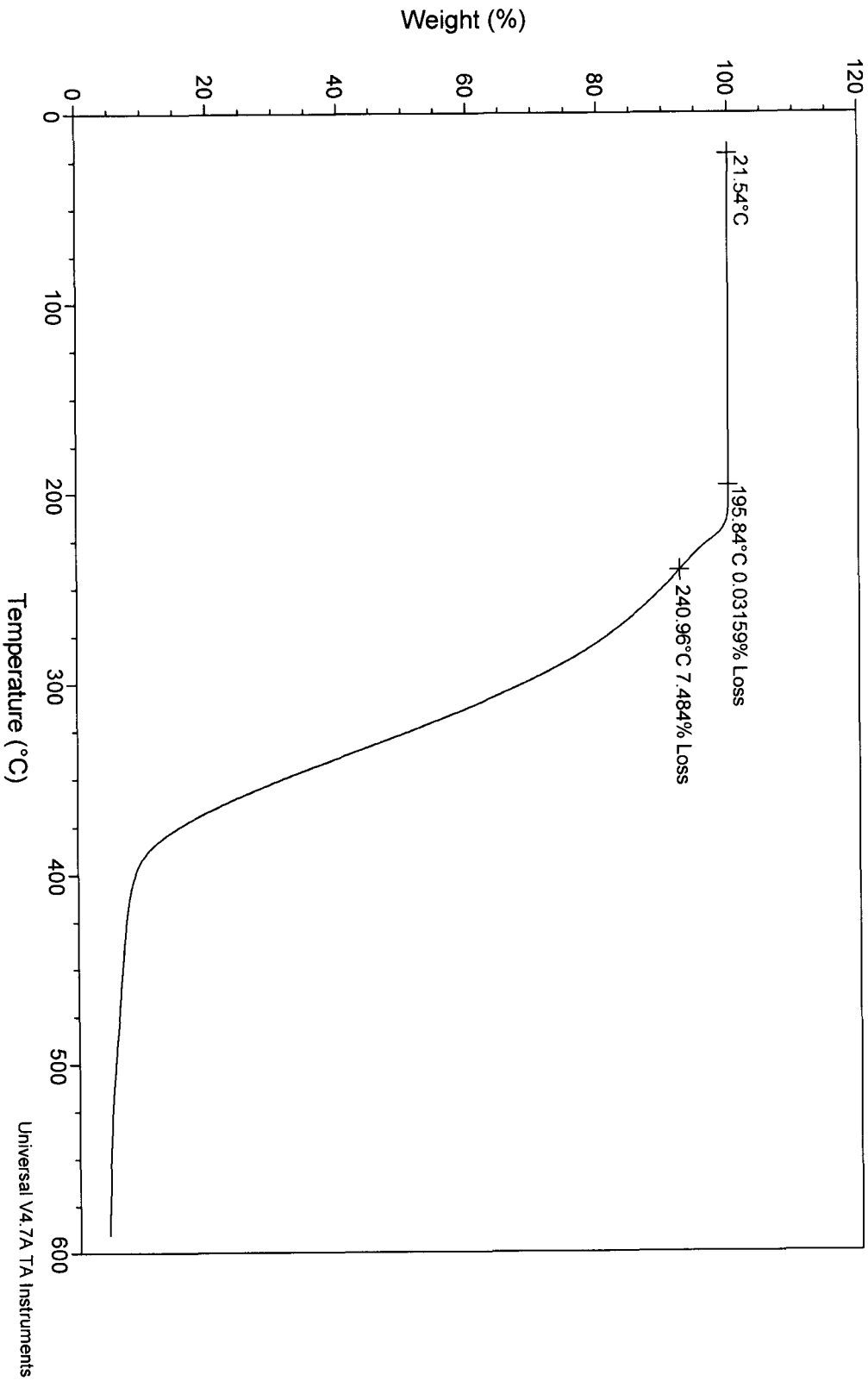


FIGURE 7. TGA profile of Form 3

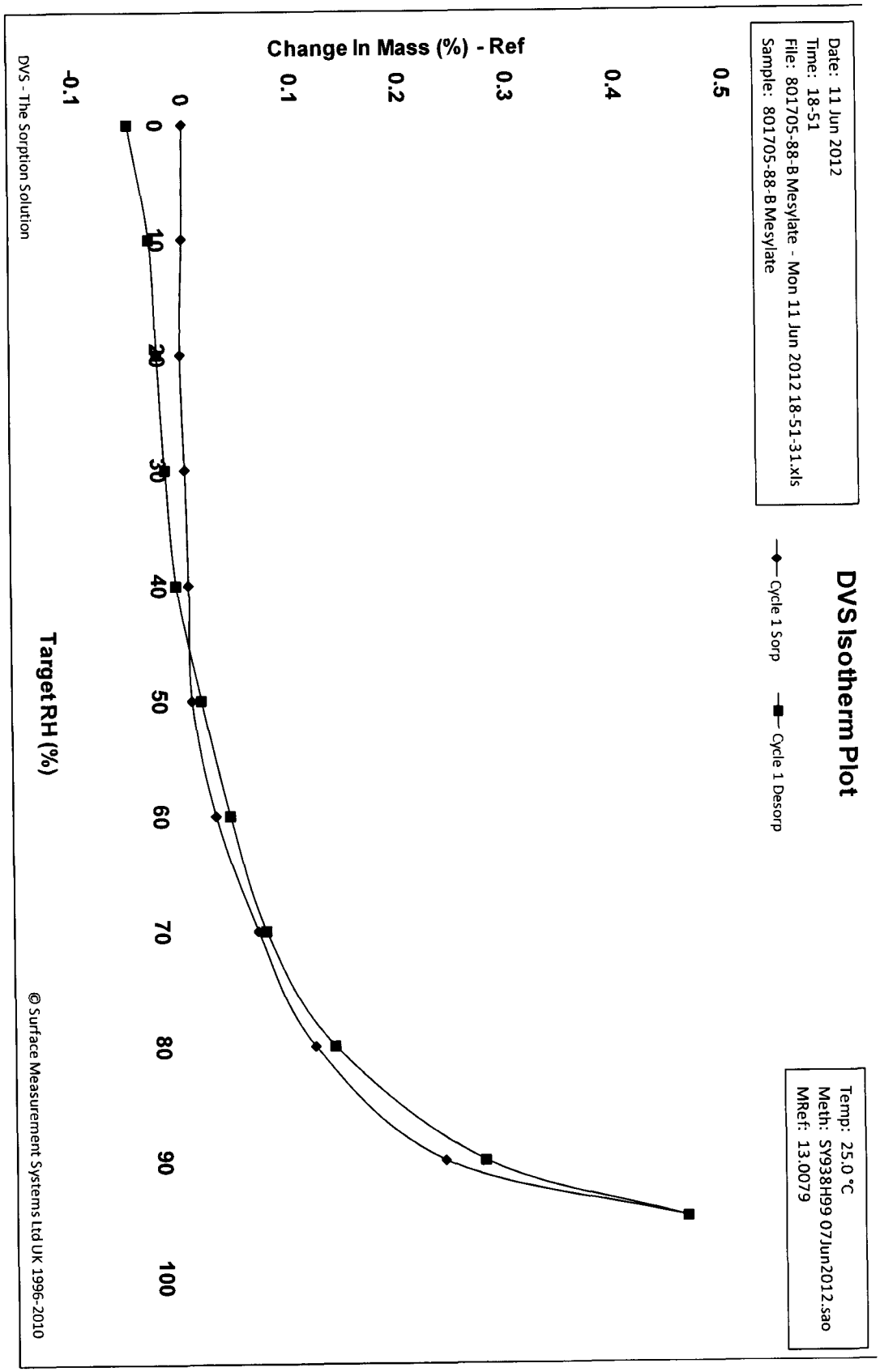


FIGURE 8. DVS profile of Form 3

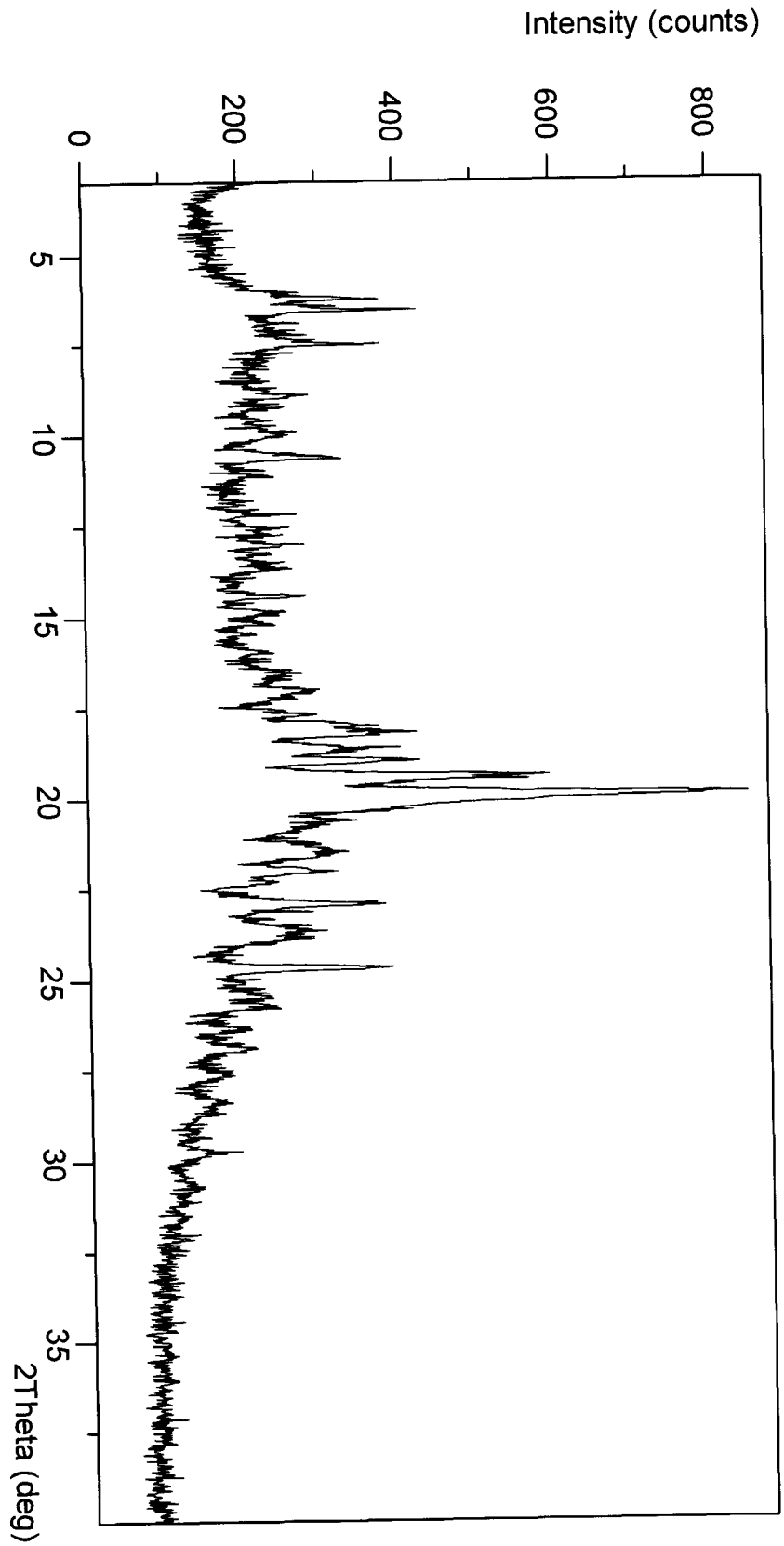


FIGURE 9. XRPD pattern of Form 4

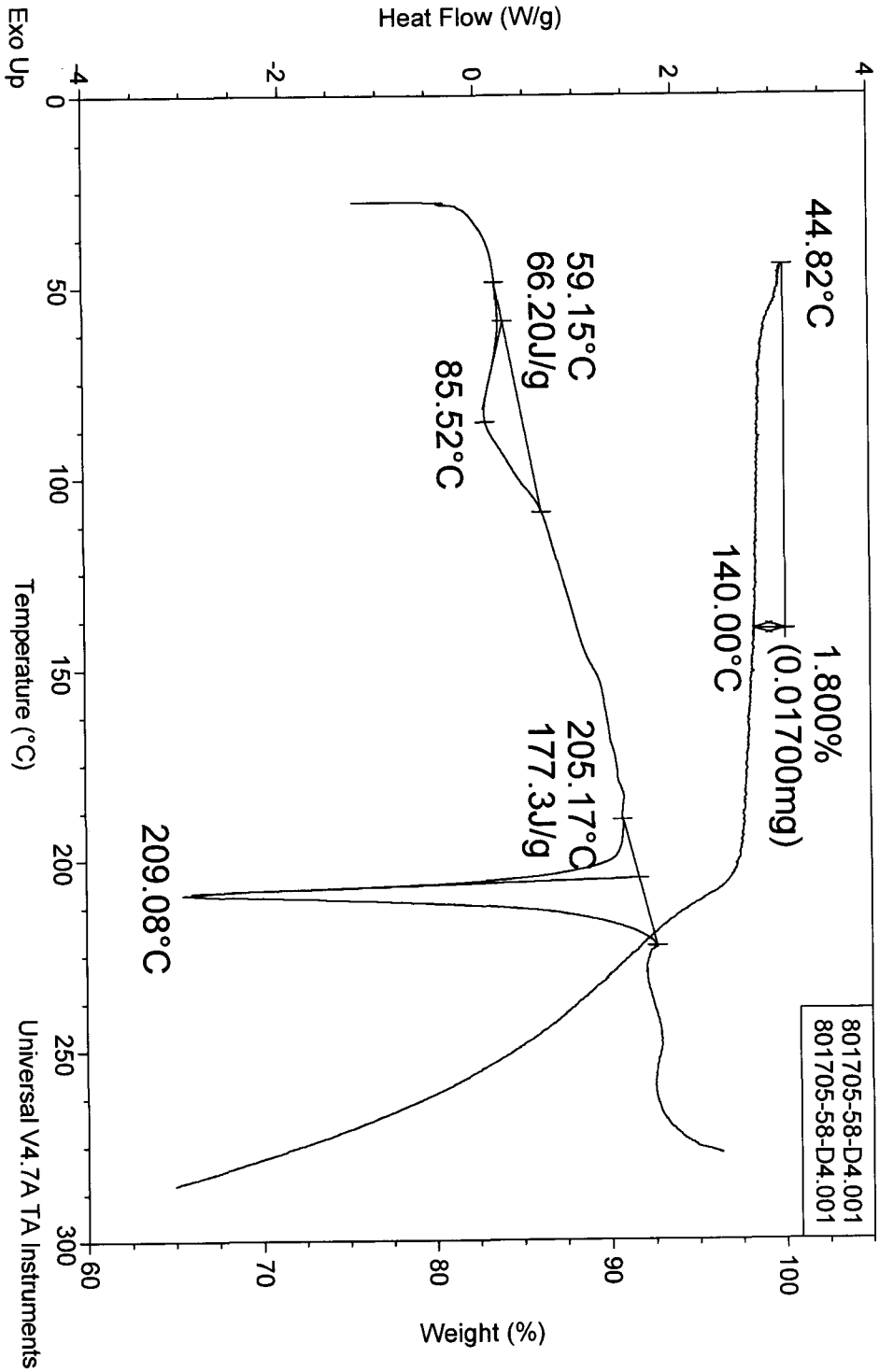


FIGURE 10. DSC and TGA profile of Form 4

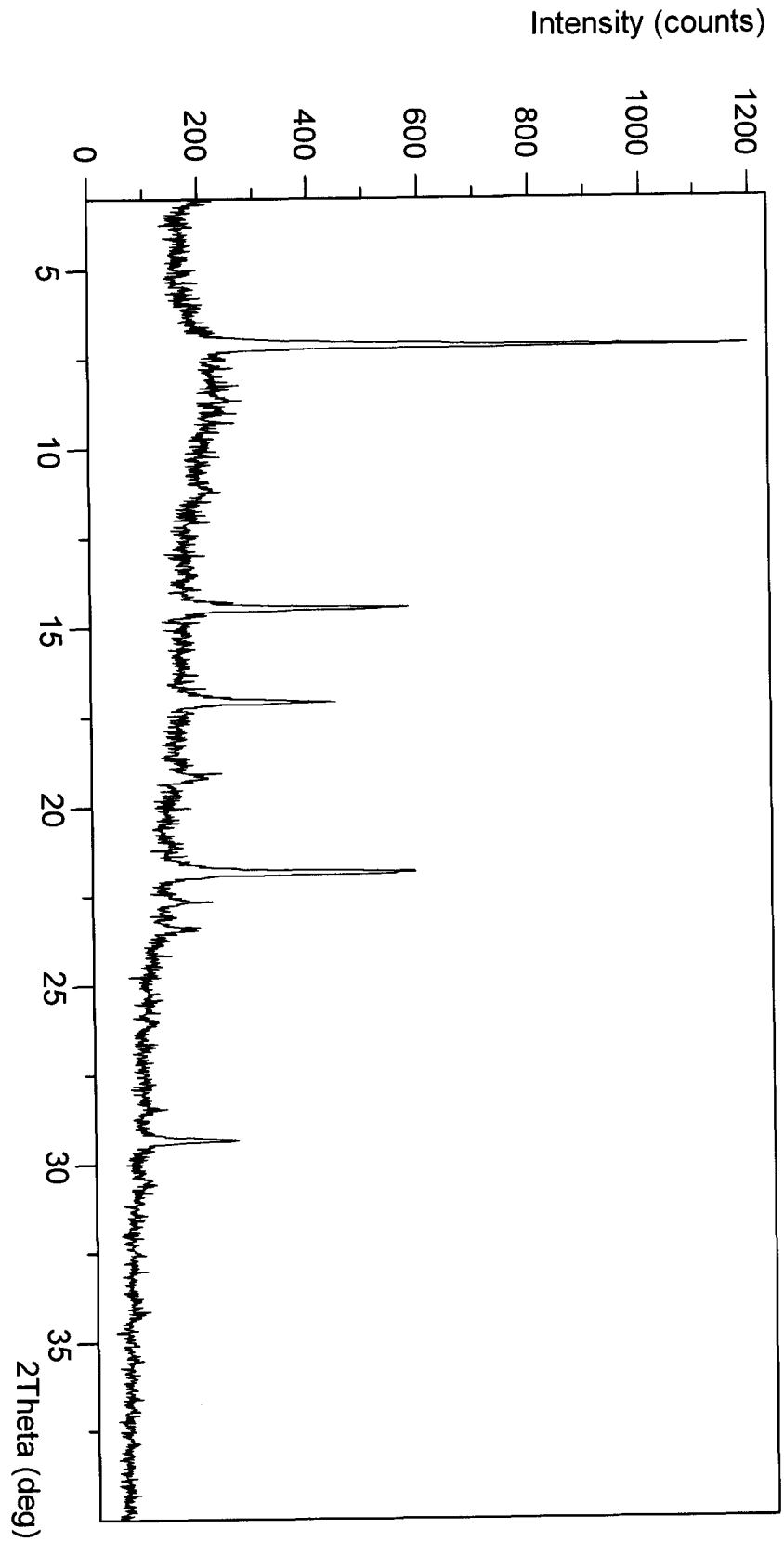


FIGURE 11. XRPD pattern of Form 5

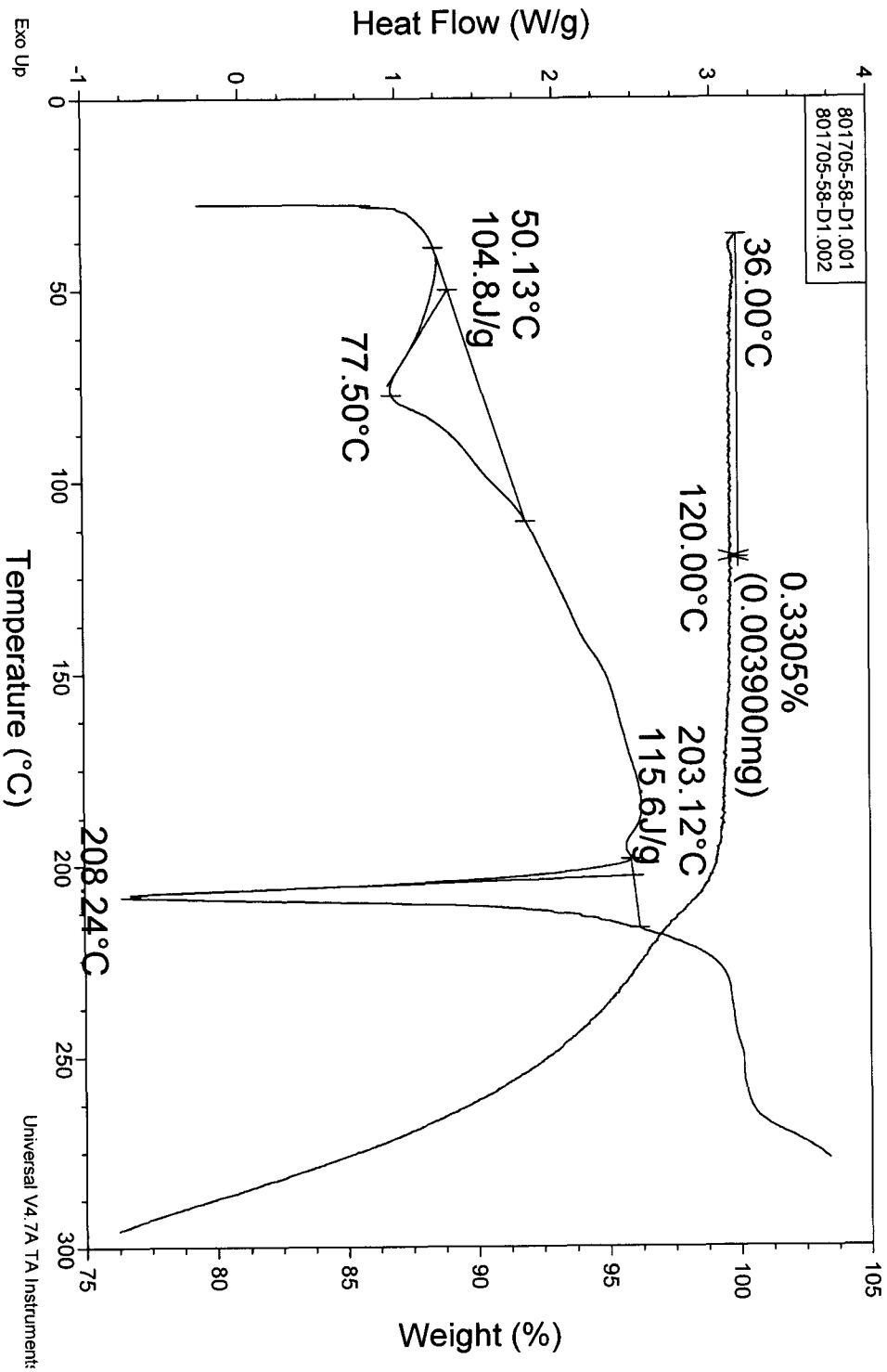


FIGURE 12. DSC and TGA profile of Form 5

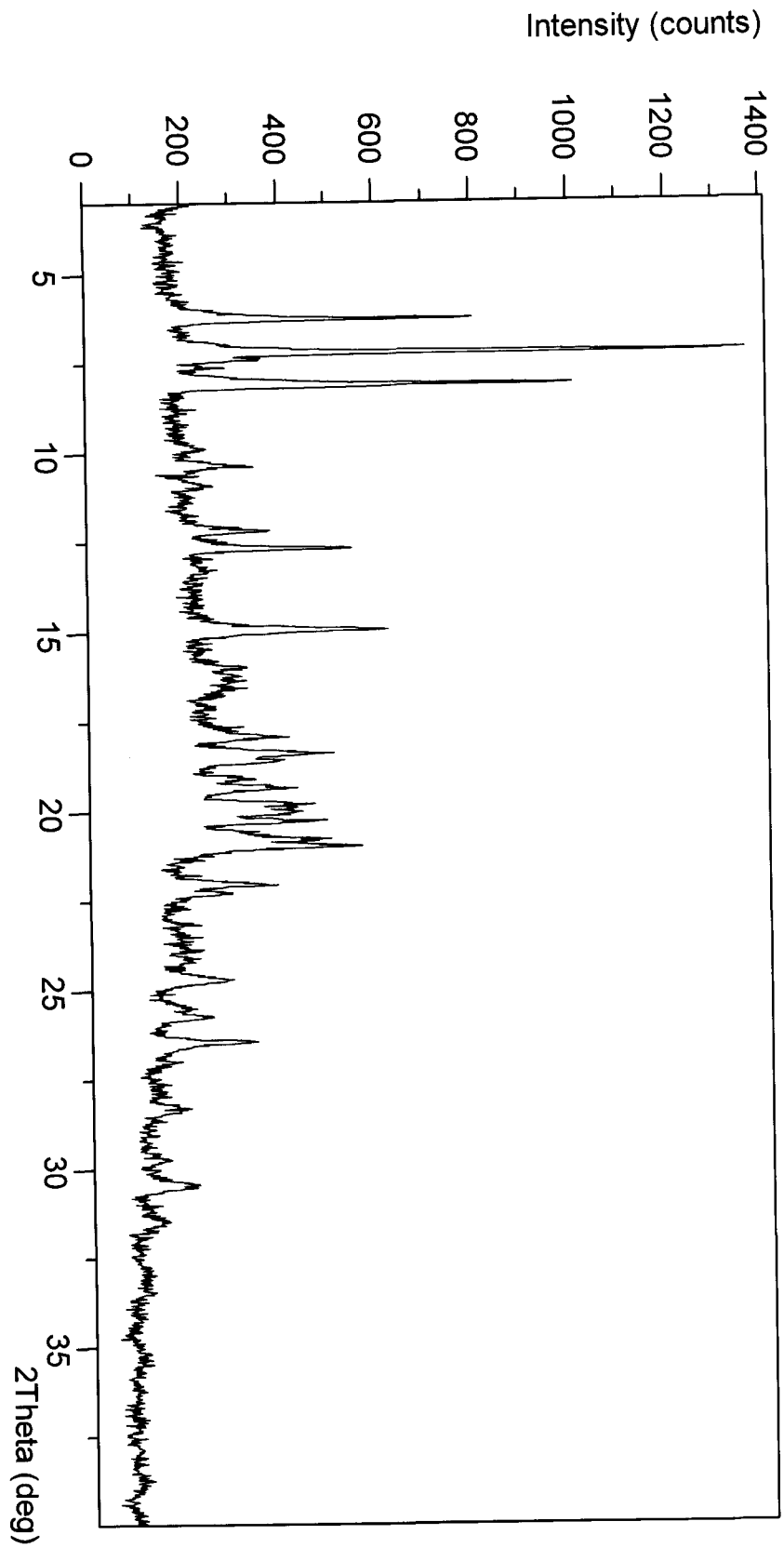


FIGURE 13. XRPD pattern of Form 6

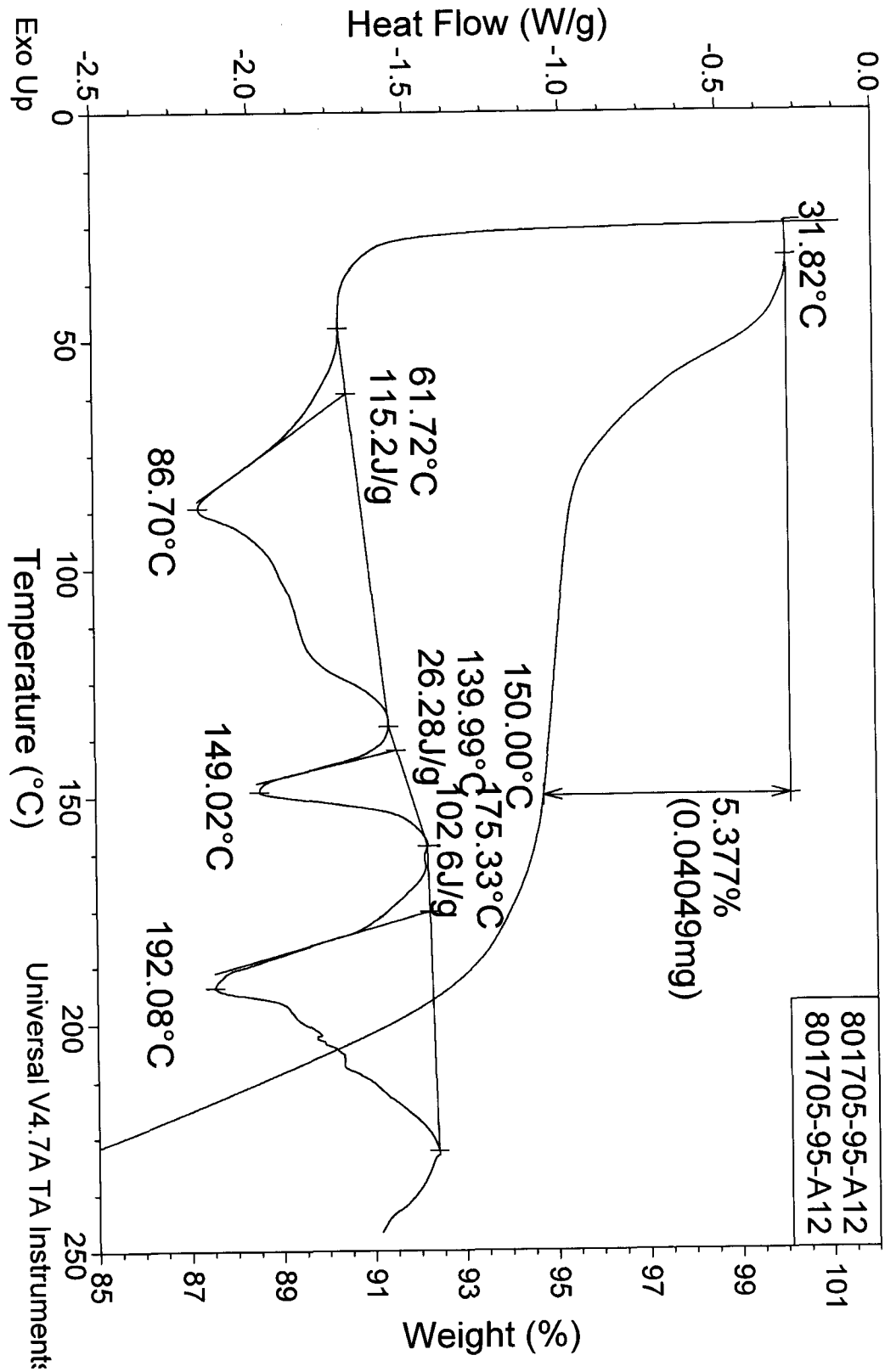


FIGURE 14. DSC and TGA profile of Form 6

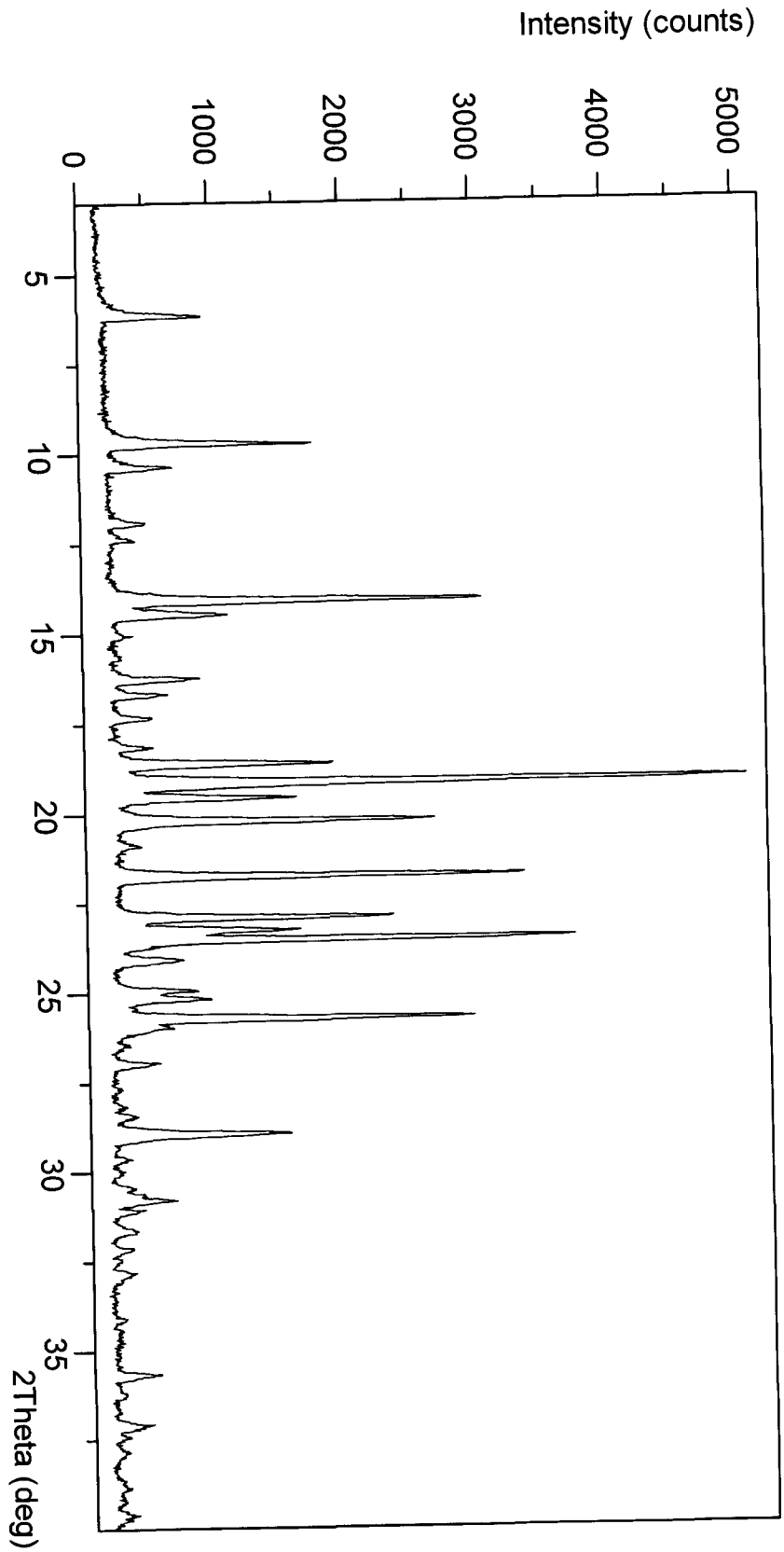


FIGURE 15. XRPD pattern of Form 7

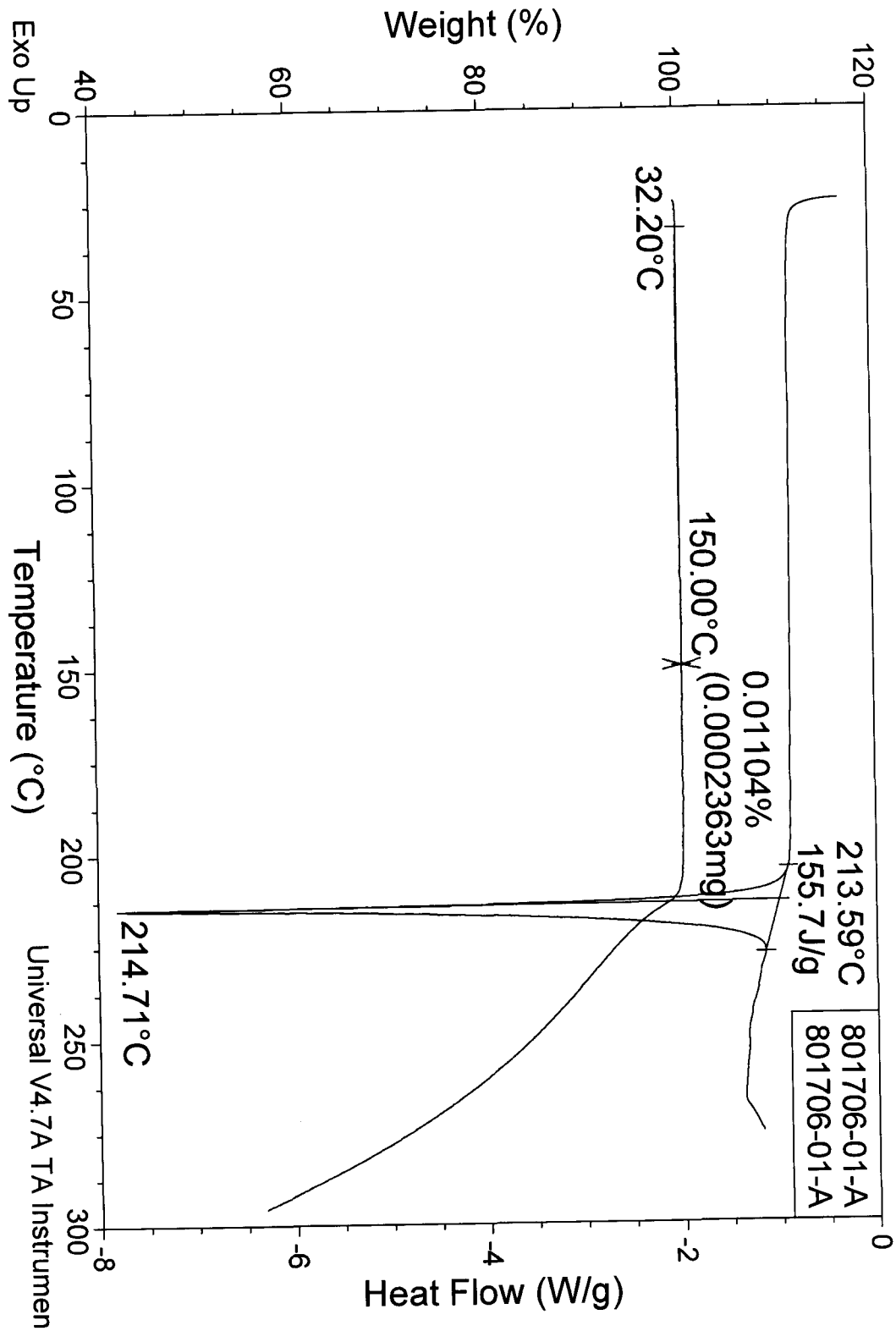


FIGURE 16. DSC and TGA profile of Form 7

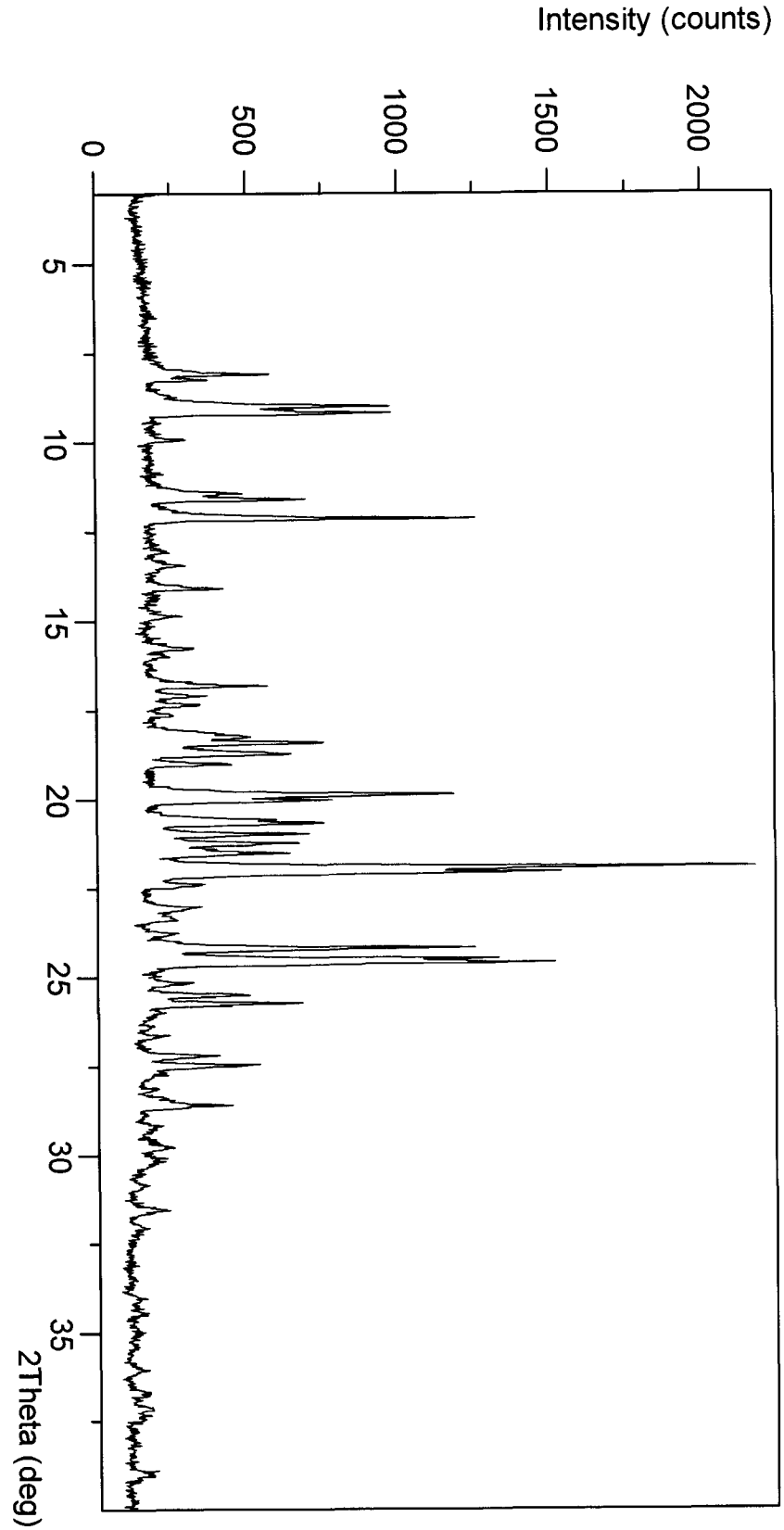


FIGURE 17. XRPD pattern of Form 8

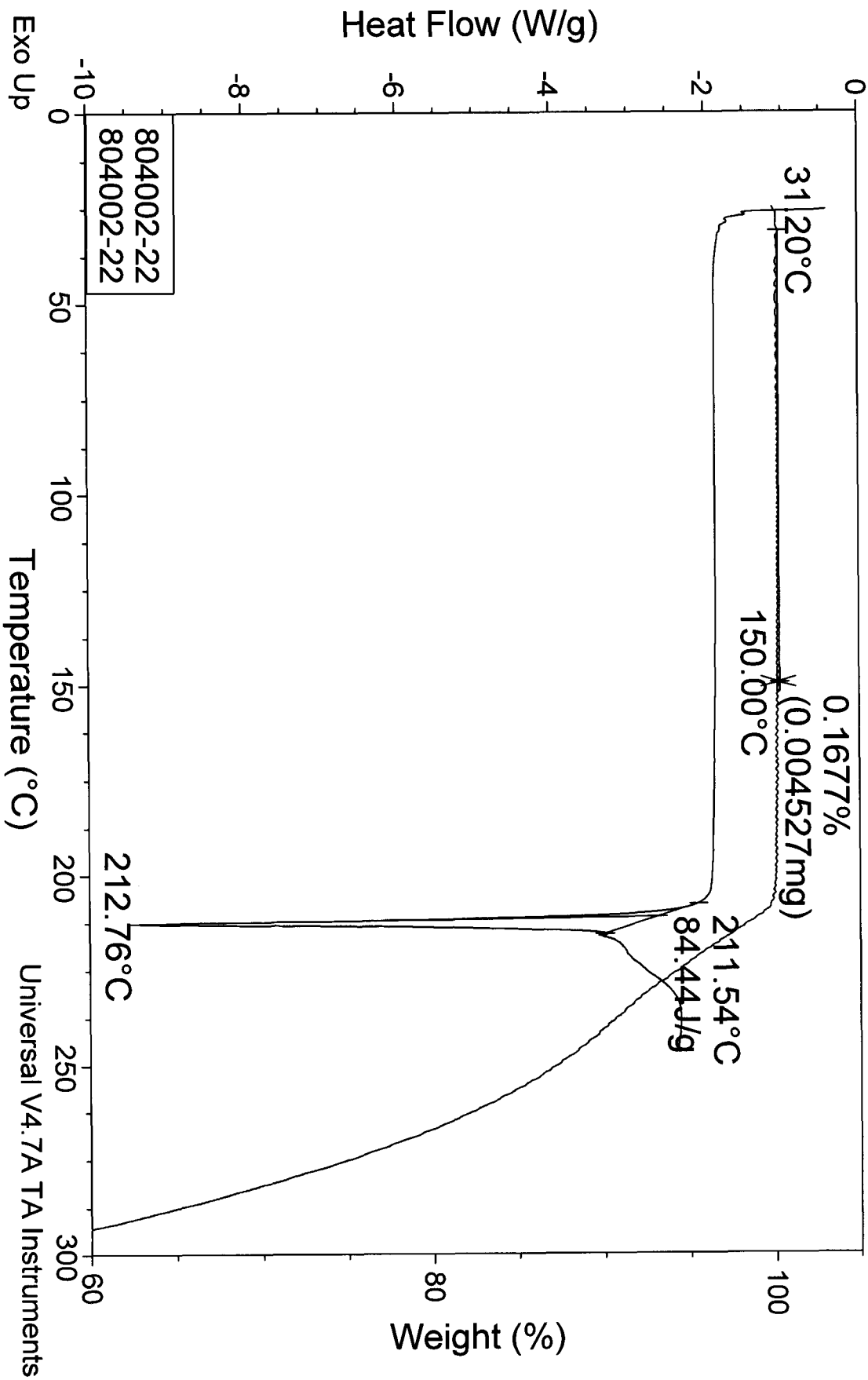


FIGURE 18. DSC and TGA profile of Form 8

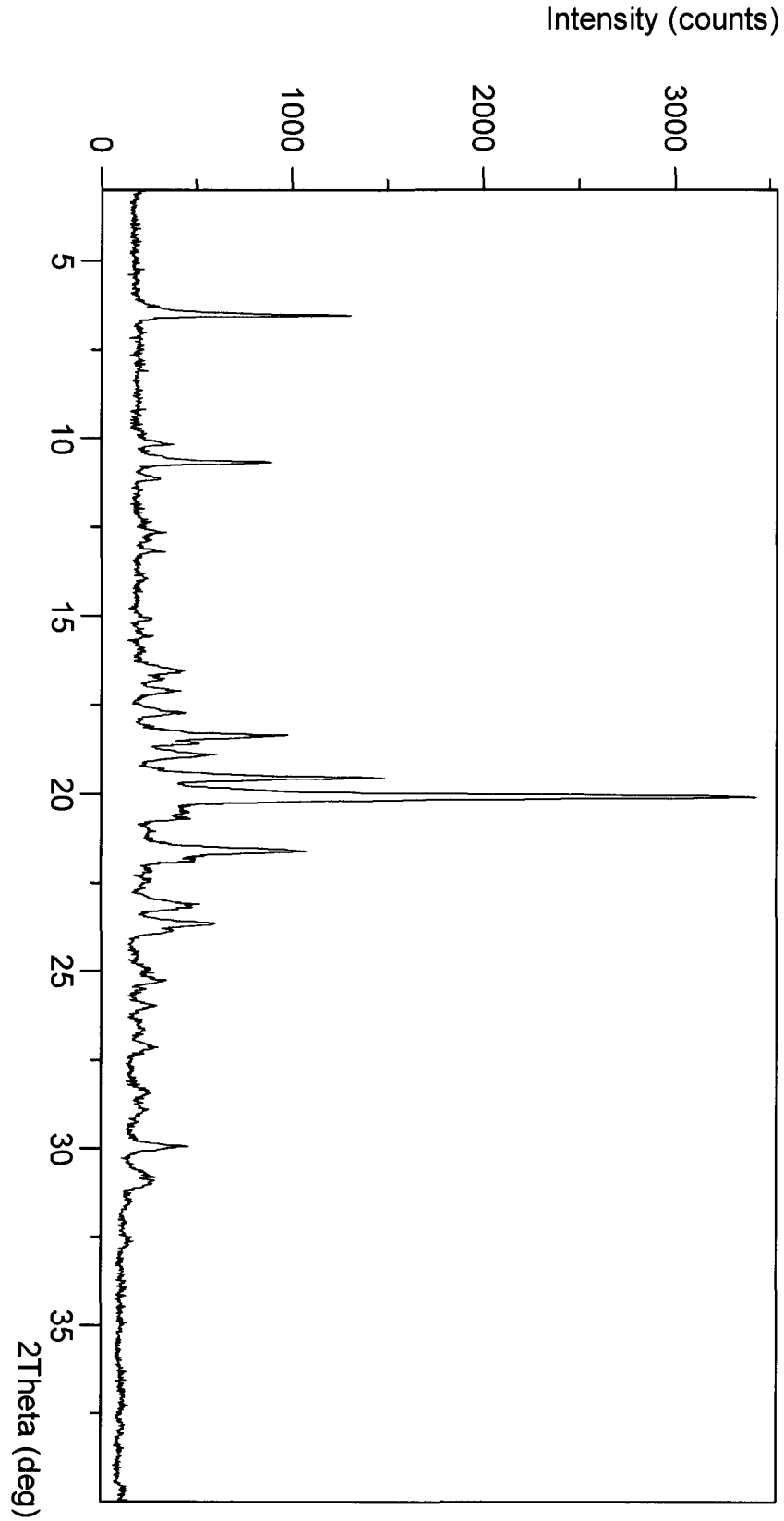


FIGURE 19. XRPD pattern of Form 9

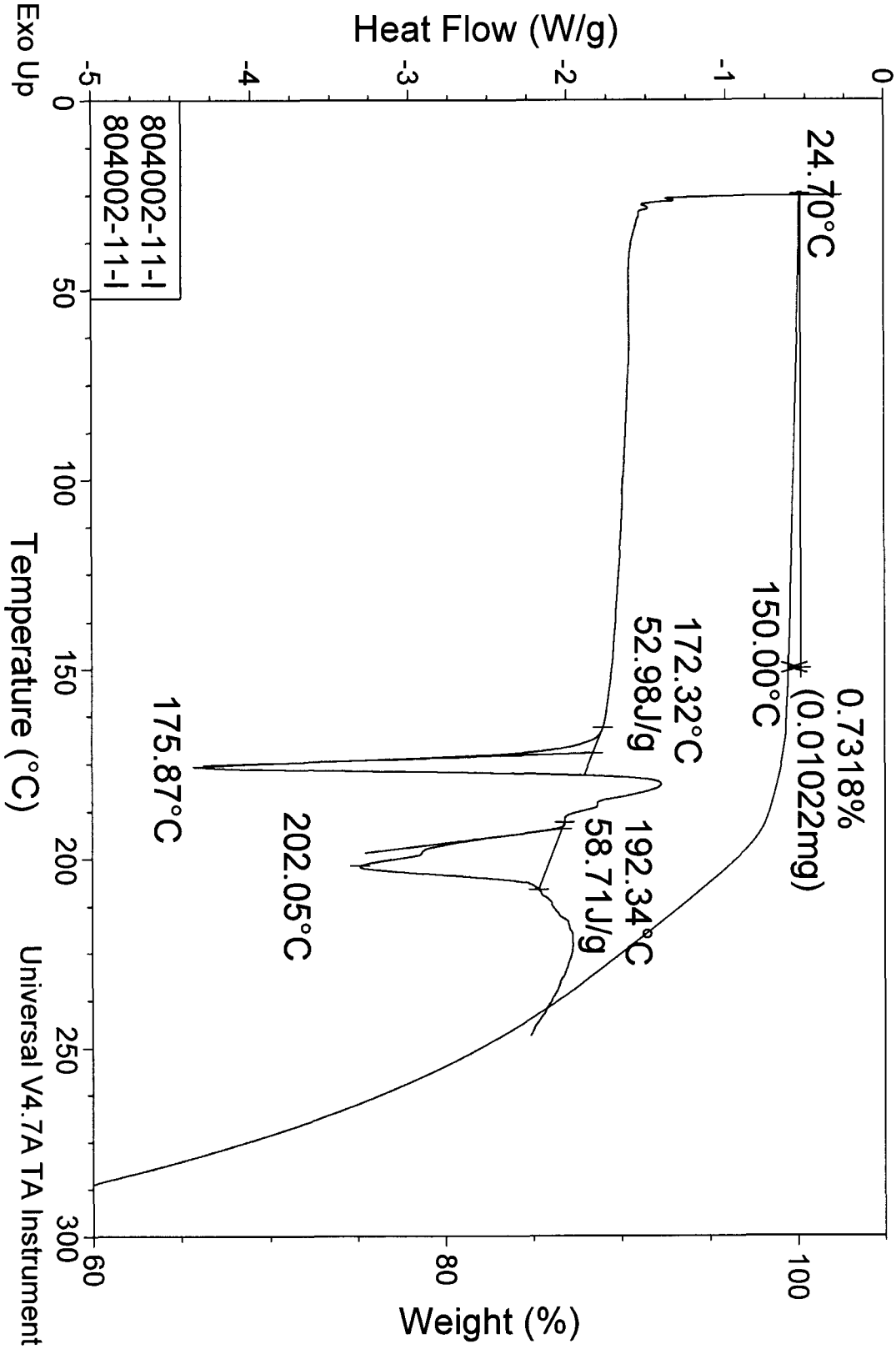


FIGURE 20. DSC and TGA profile of Form 9

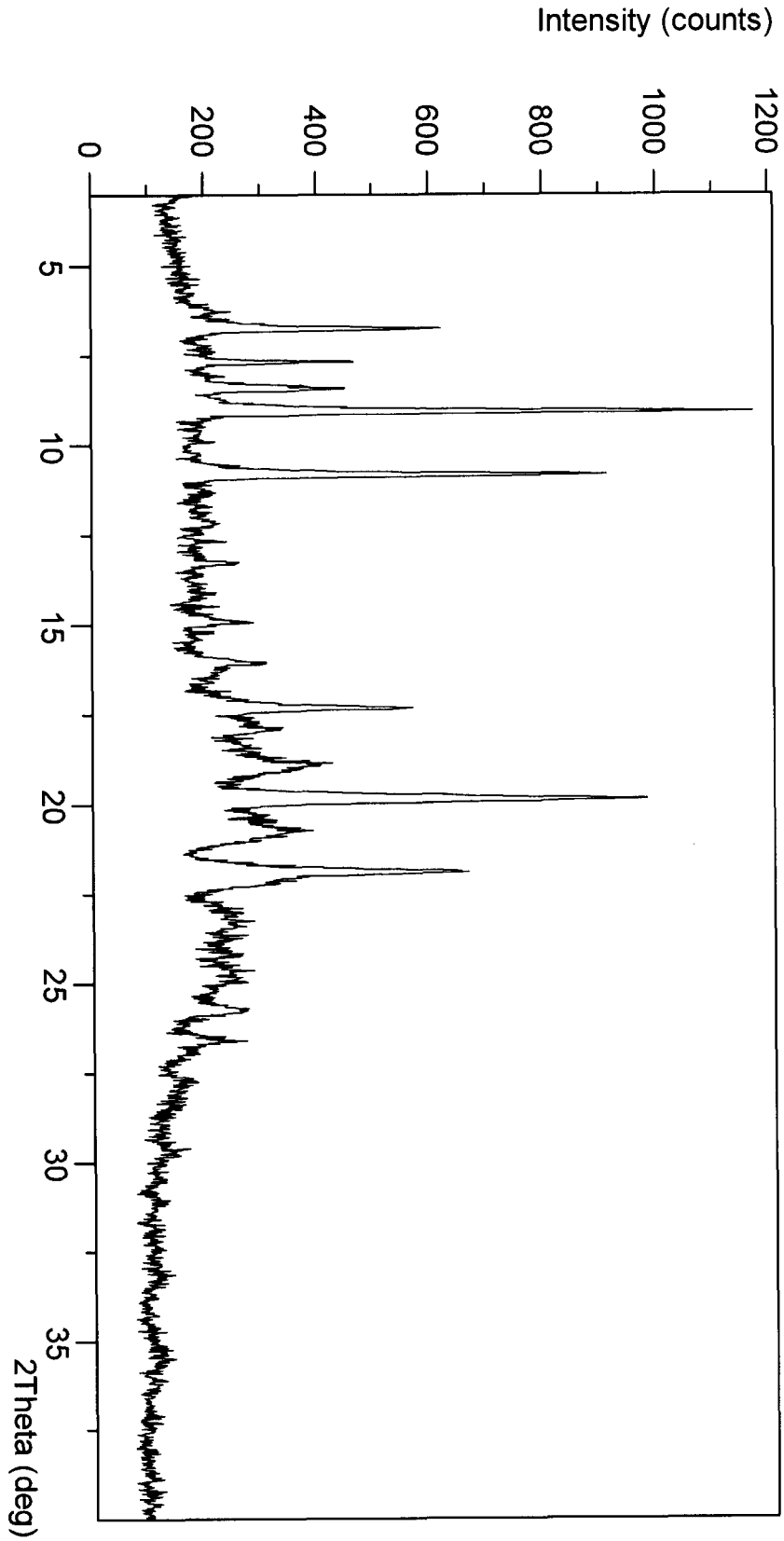


FIGURE 21. XRPD pattern of Form 10

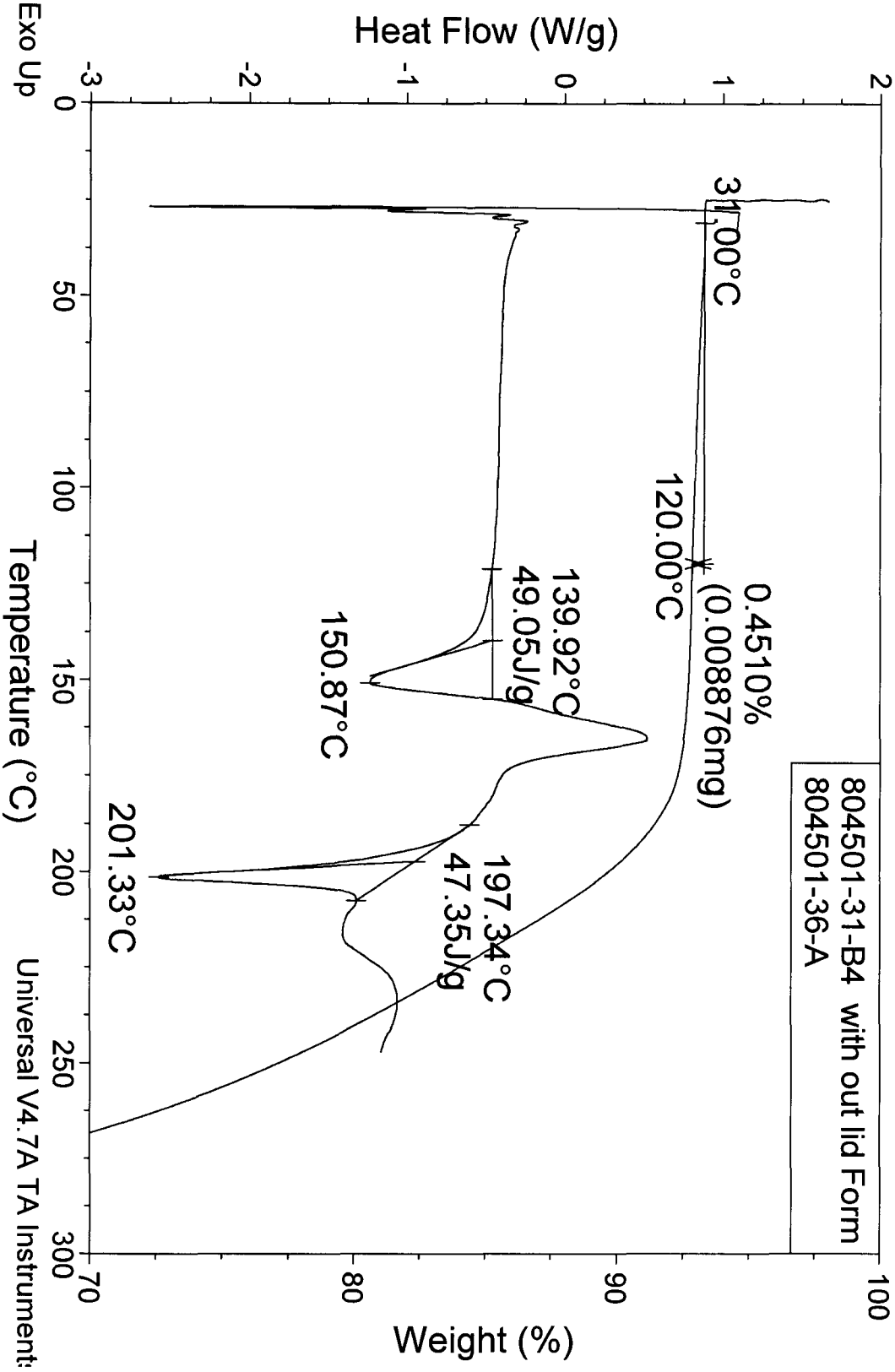


FIGURE 22. DSC and TGA profile of Form 10

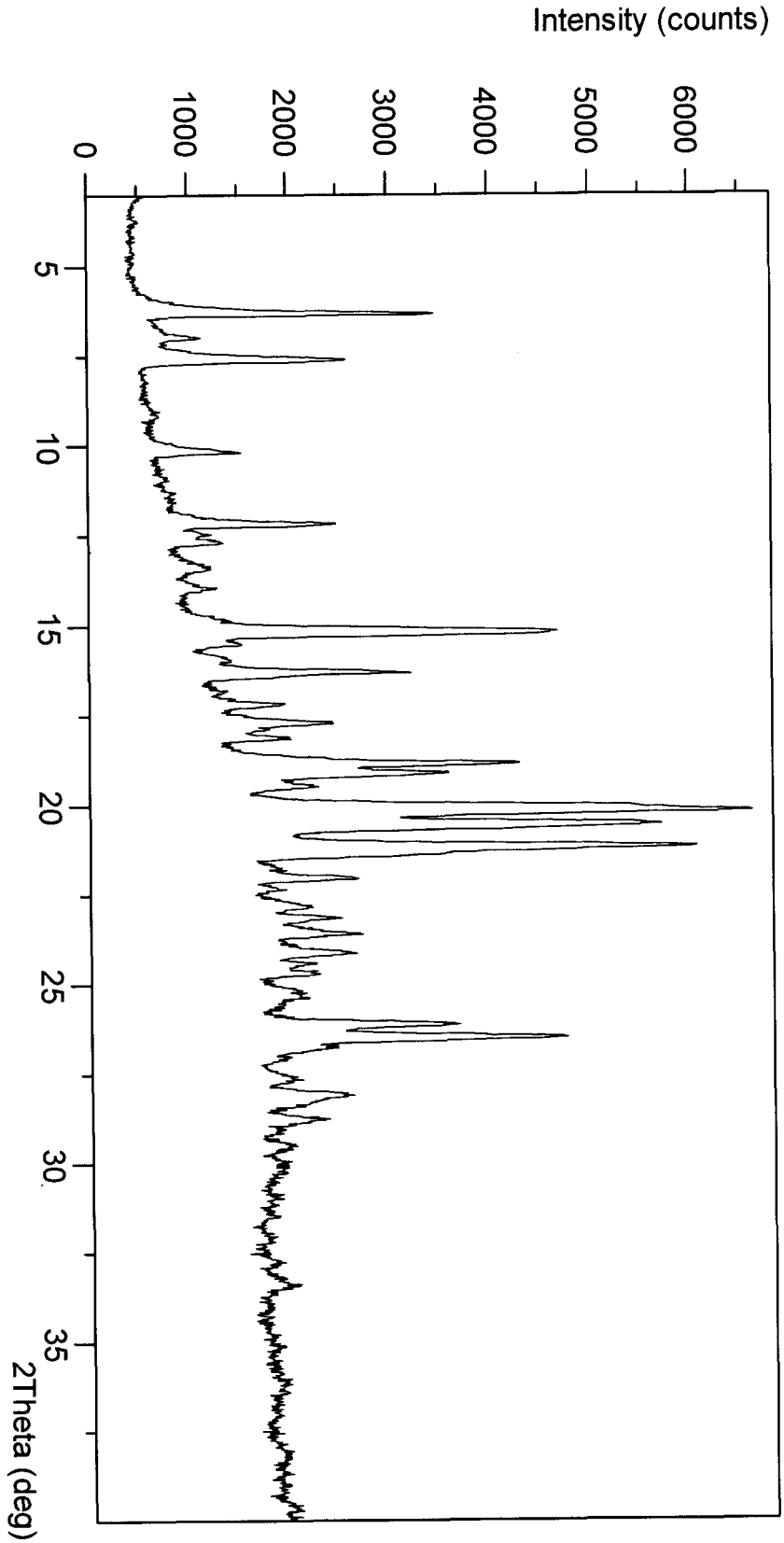


FIGURE 23. XRPD pattern of Form 11

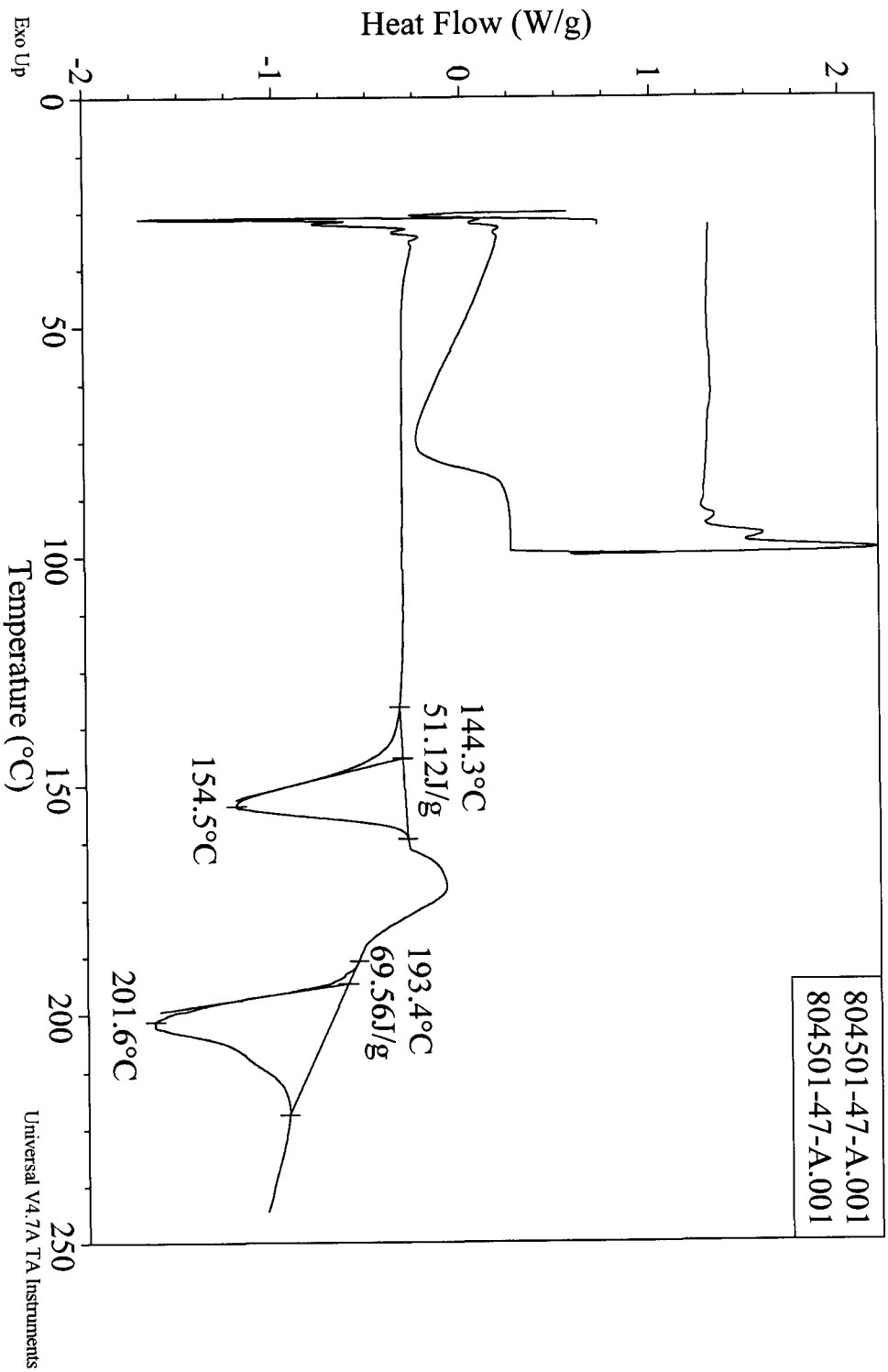


FIGURE 24. DSC profile of Form 11

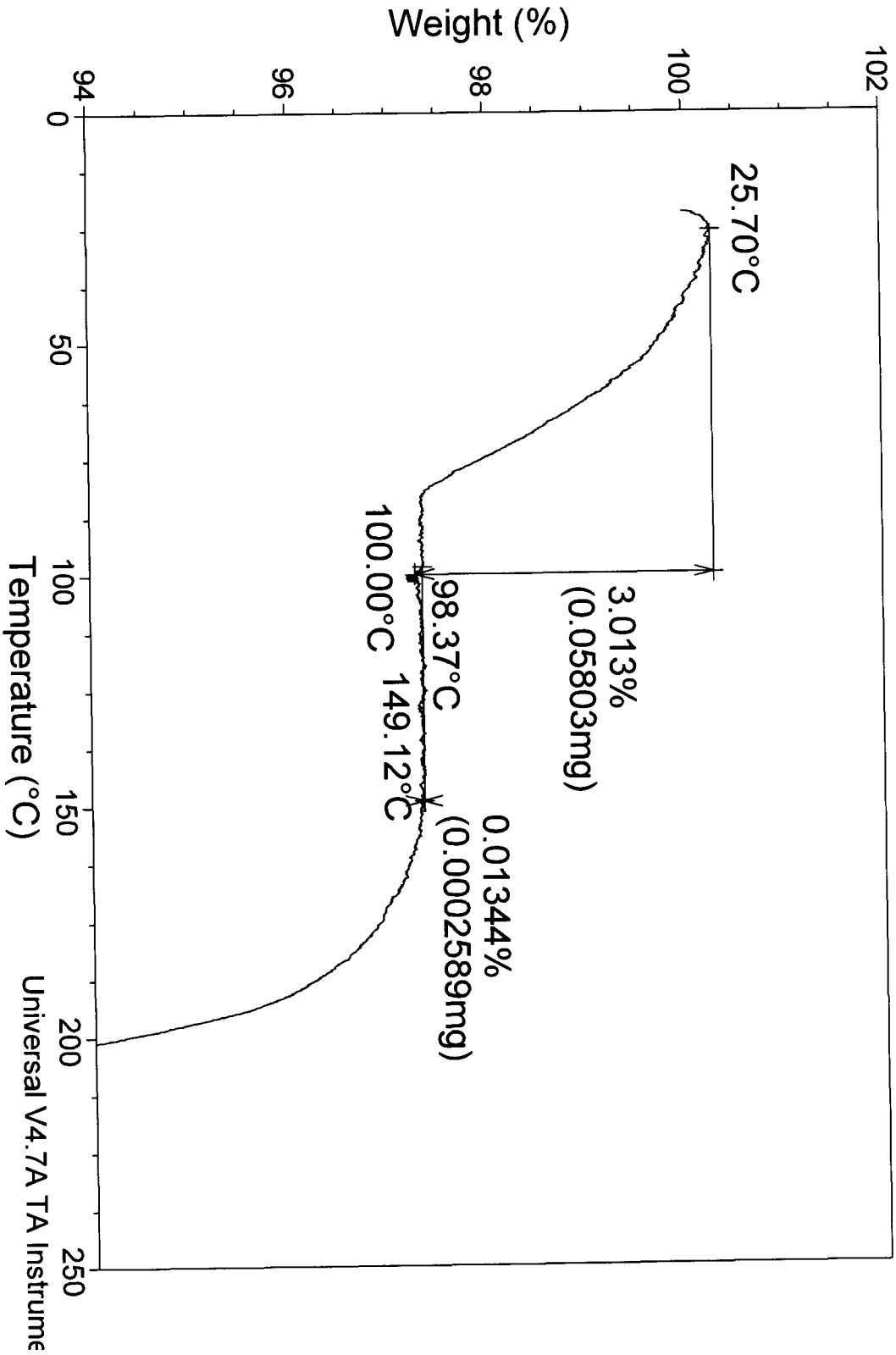


FIGURE 25. TGA profile of Form 11

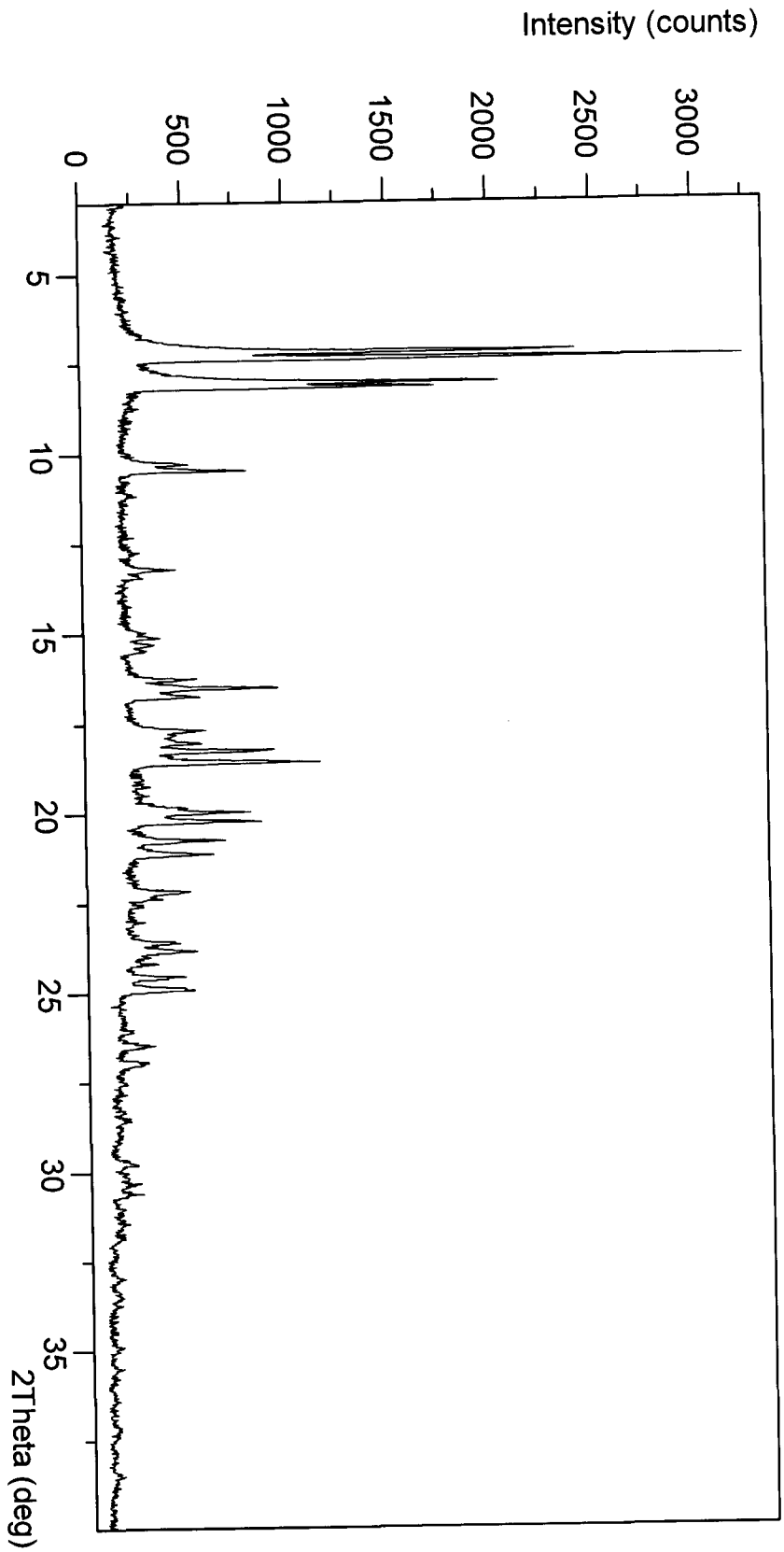


FIGURE 26. TGA profile of Form 12

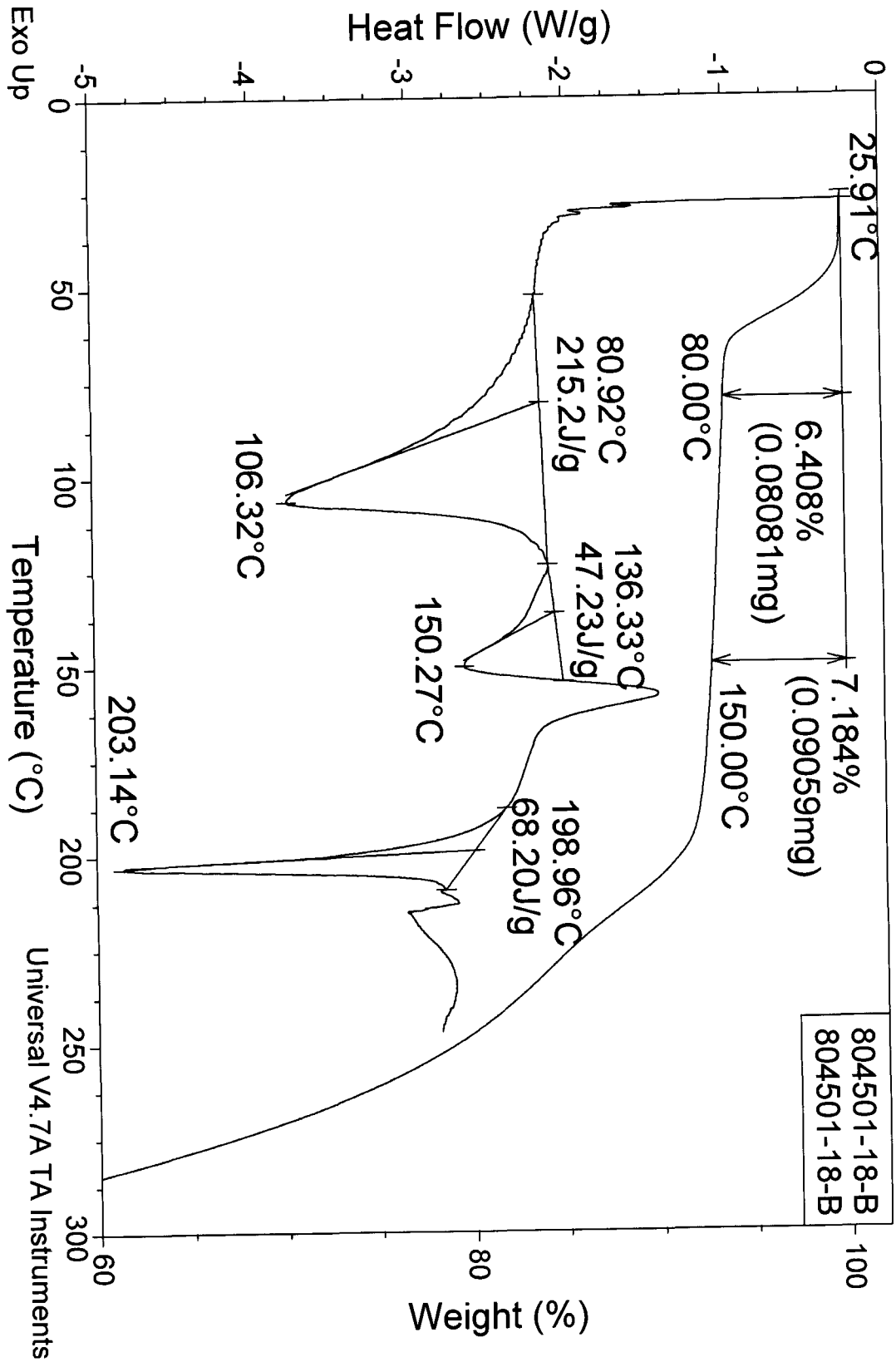


FIGURE 27. DSC and TGA profile of Form 12

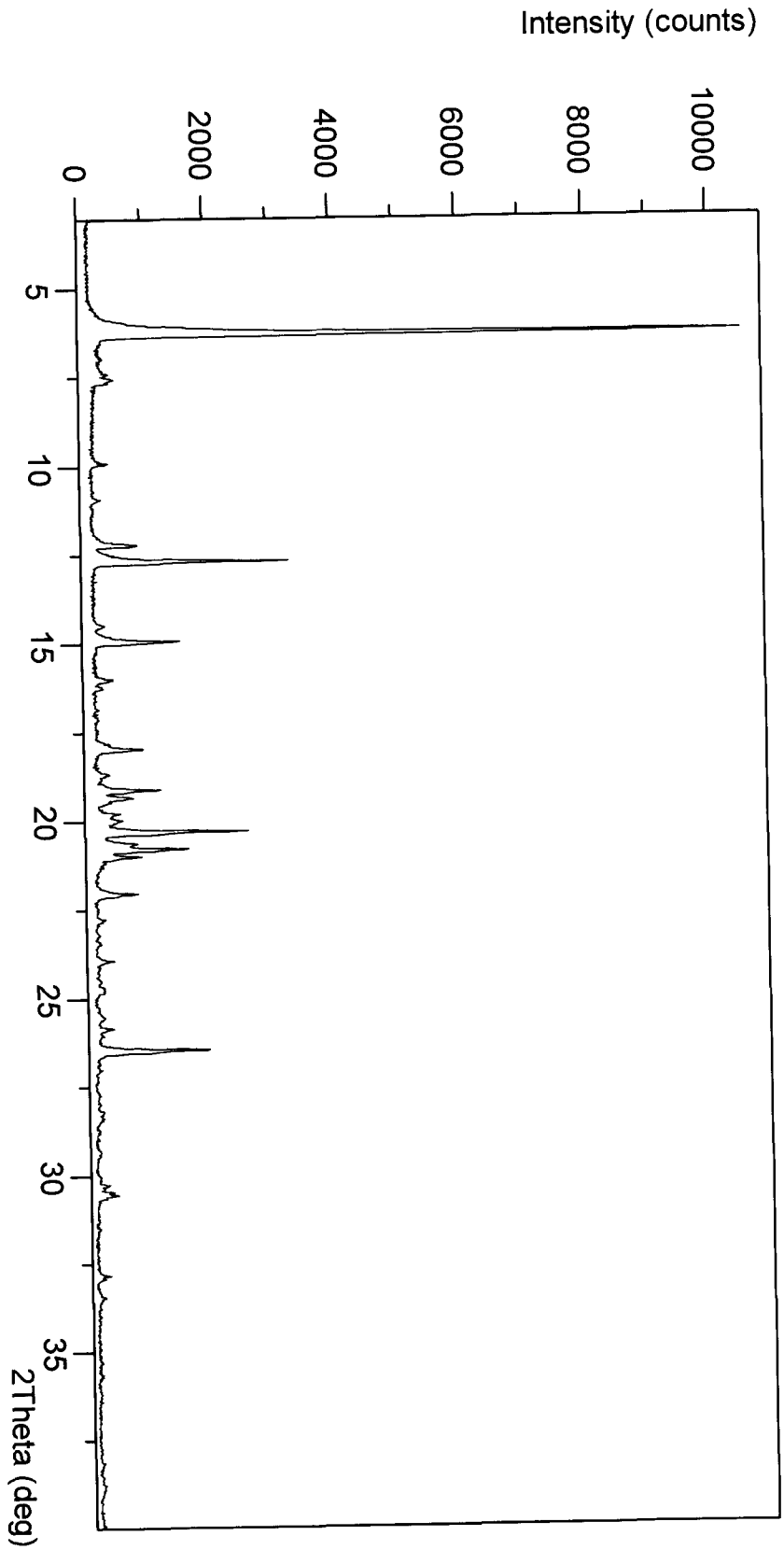


FIGURE 28. XRPD pattern of Form 13

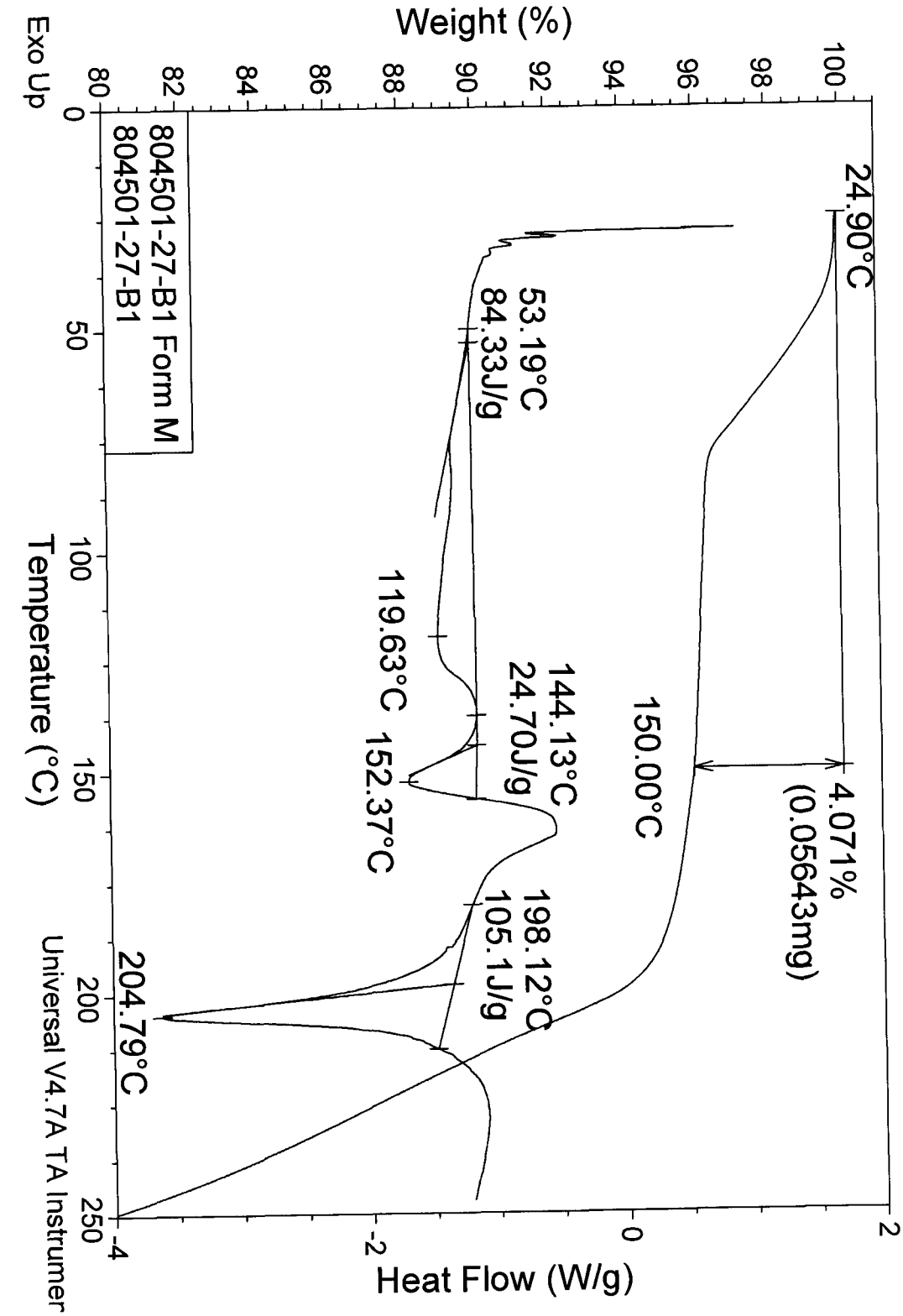


FIGURE 29. DSC and TGA profile of Form 13

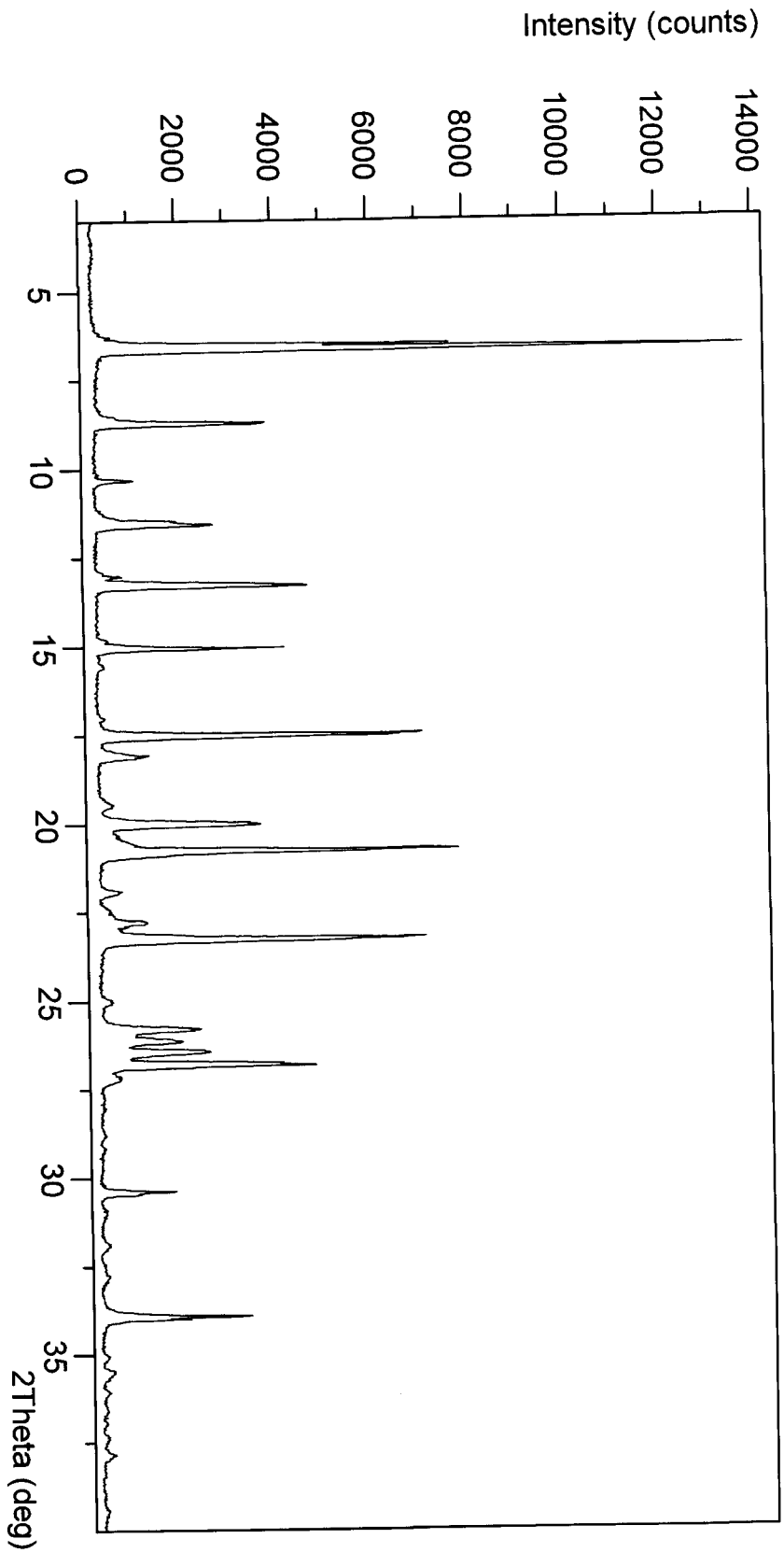


FIGURE 30. XRPD pattern of Form 14

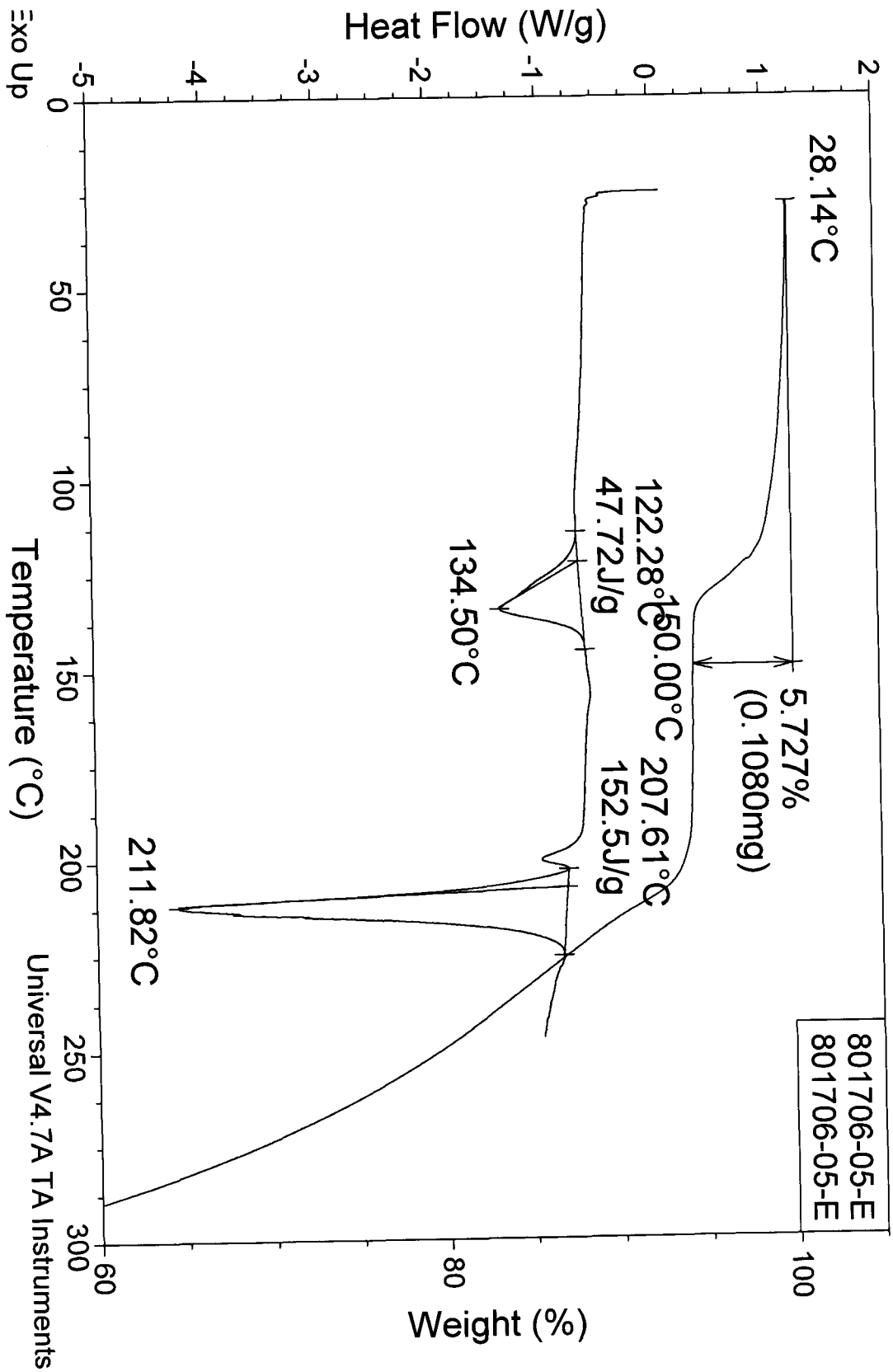


FIGURE 31. DSC and TGA profile of Form 14

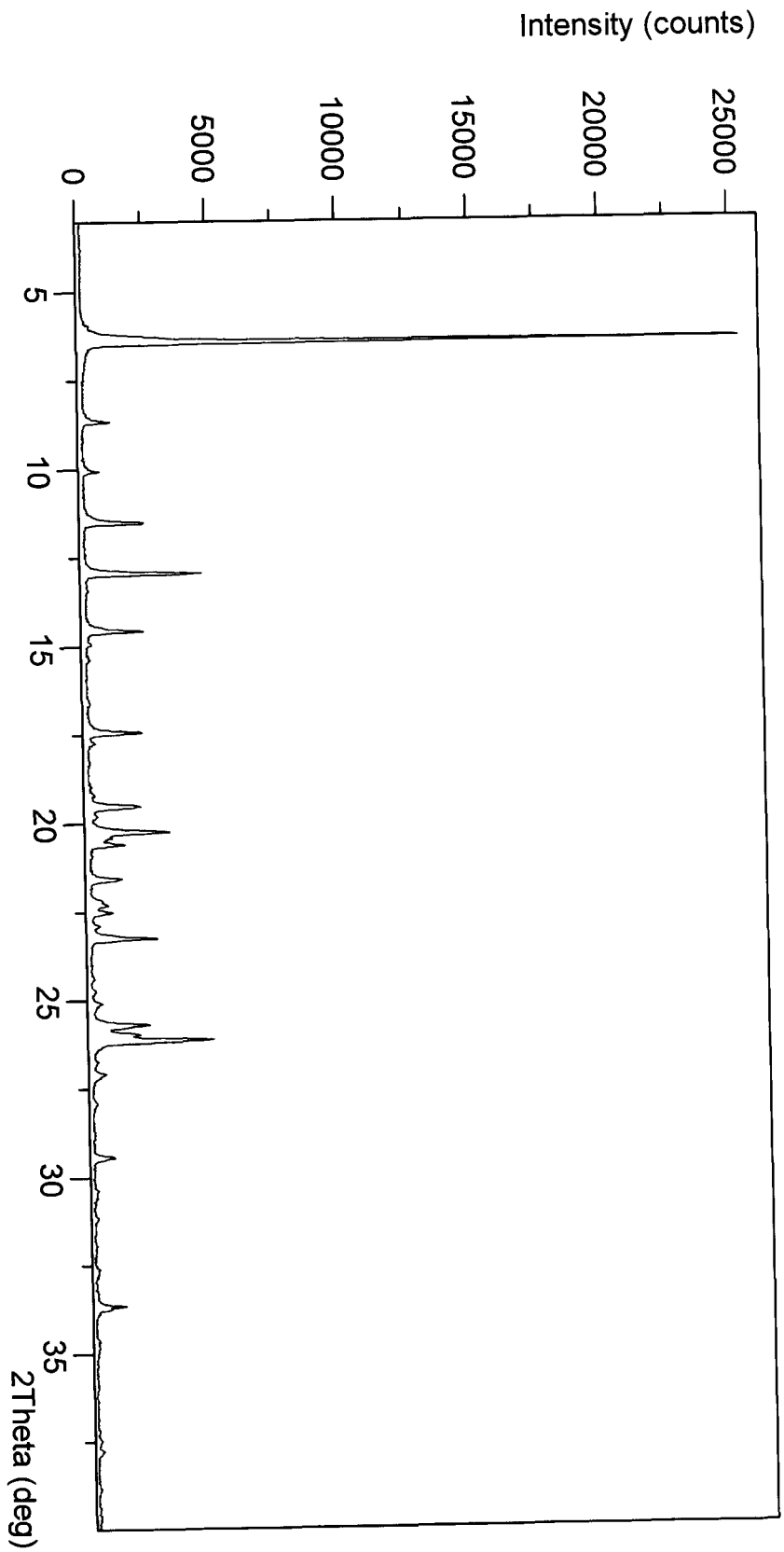


FIGURE 32. XRPD pattern of Form 15

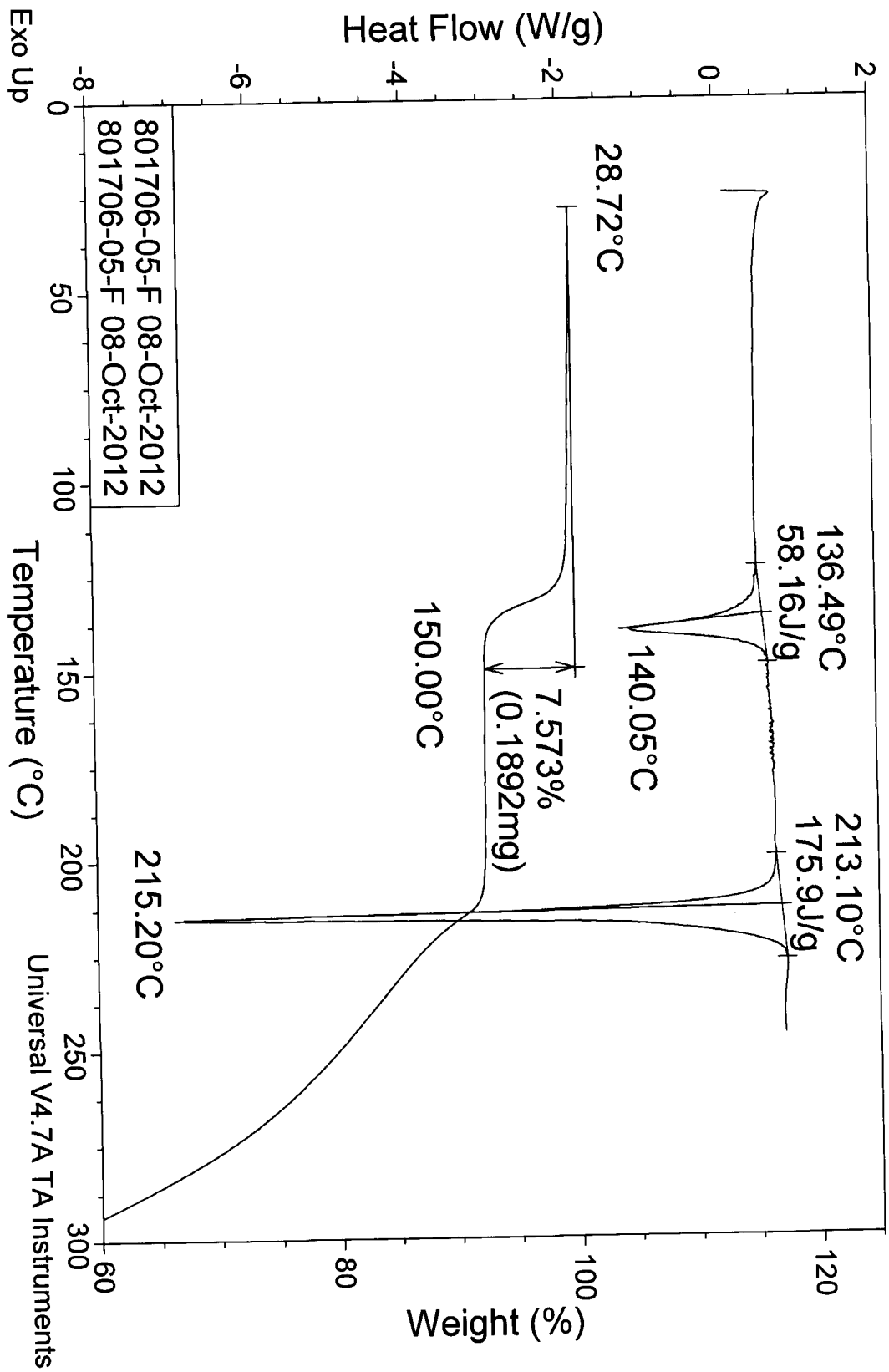


FIGURE 33. DSC and TGA profile of Form 15

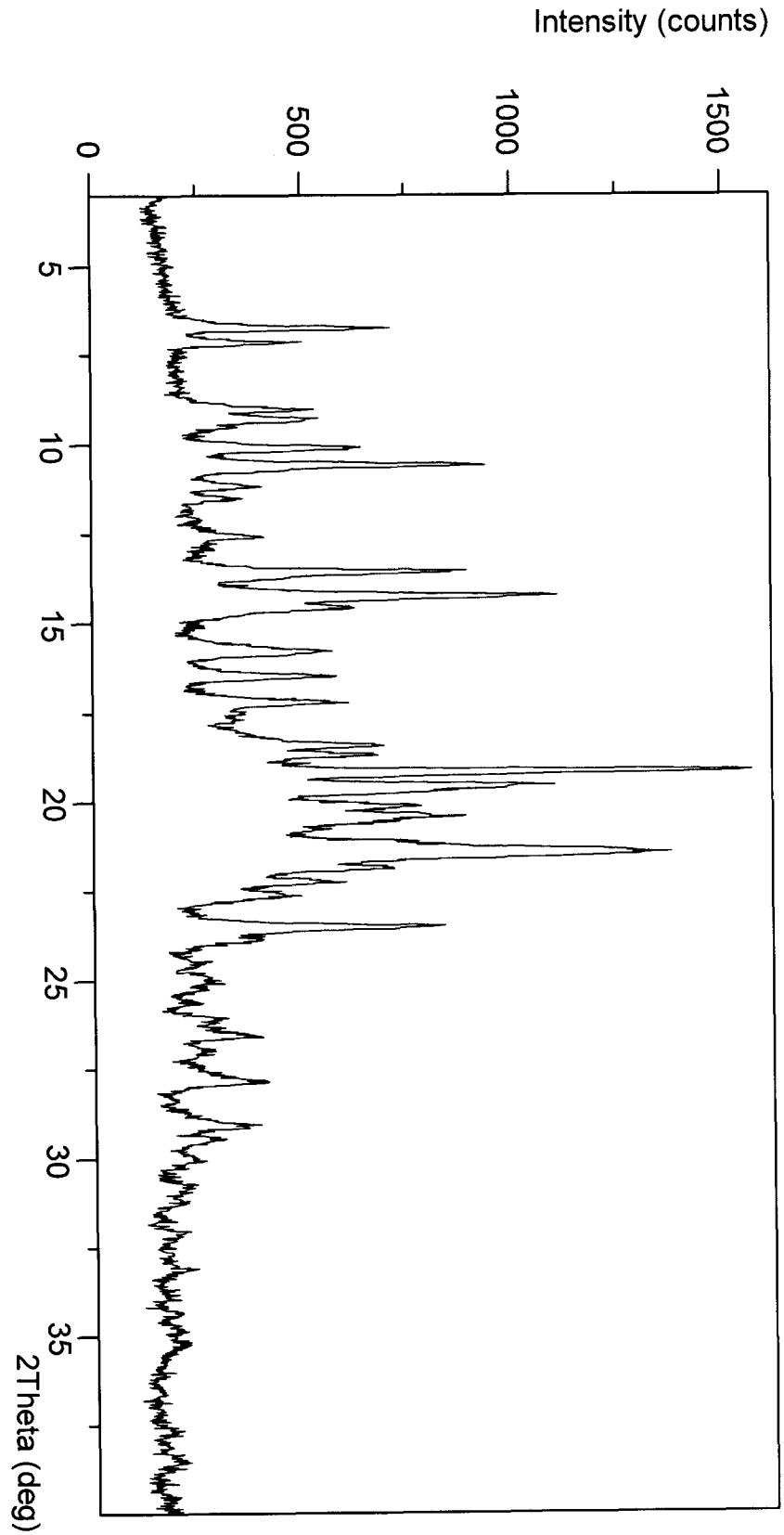


FIGURE 34. XRPD pattern of Form 16

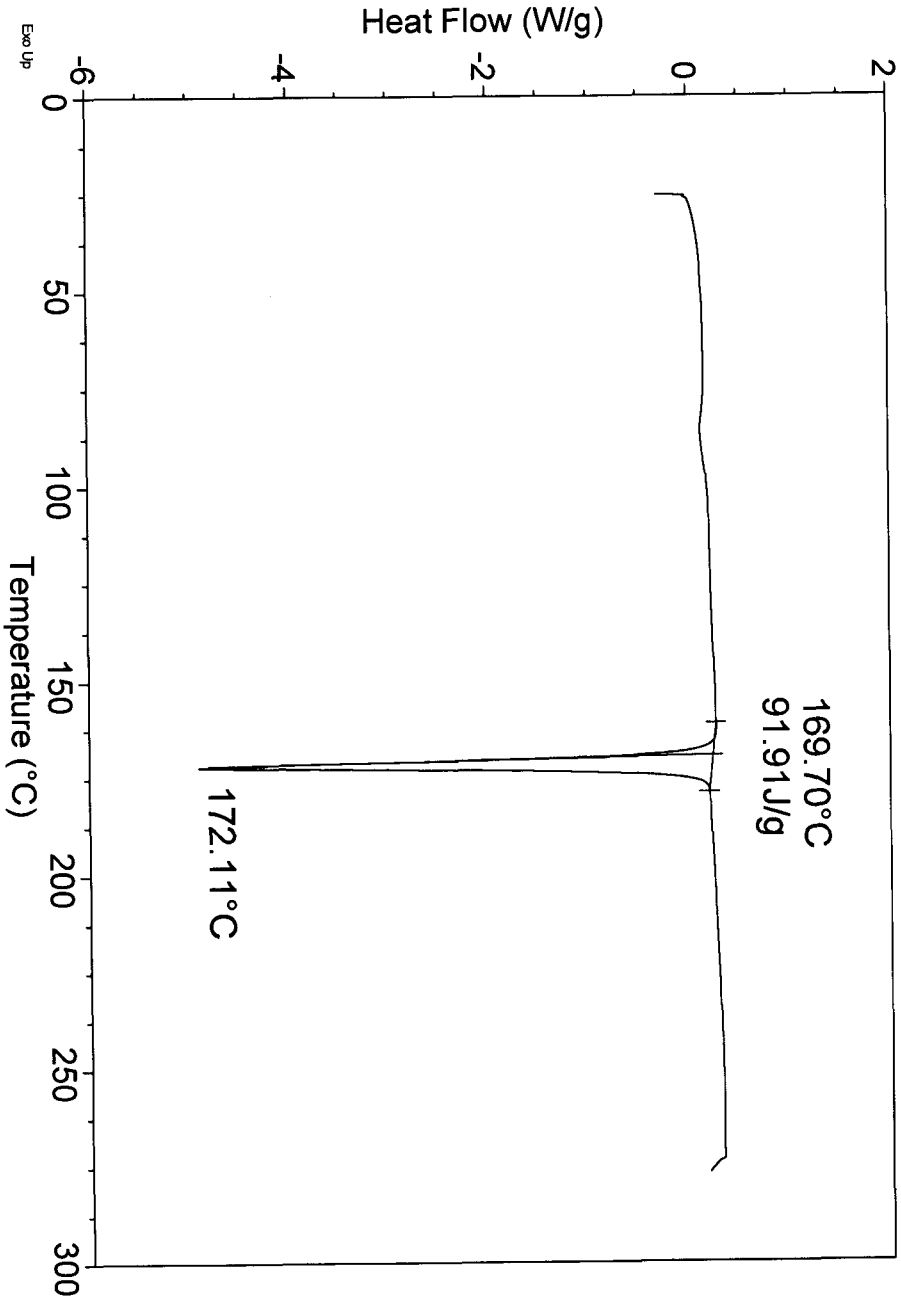


FIGURE 35. DSC profile of Form 16

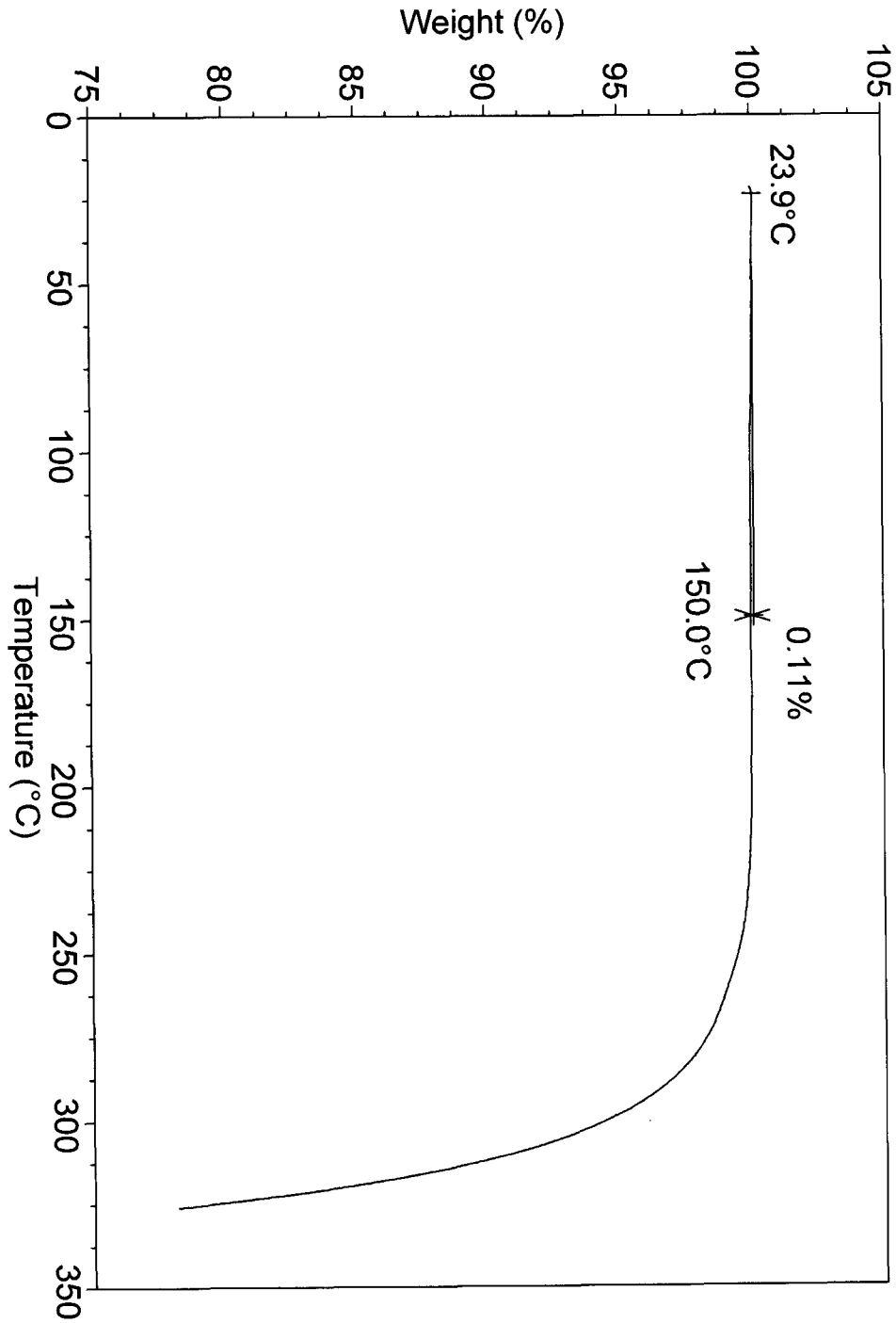


FIGURE 36. TGA profile of Form 16

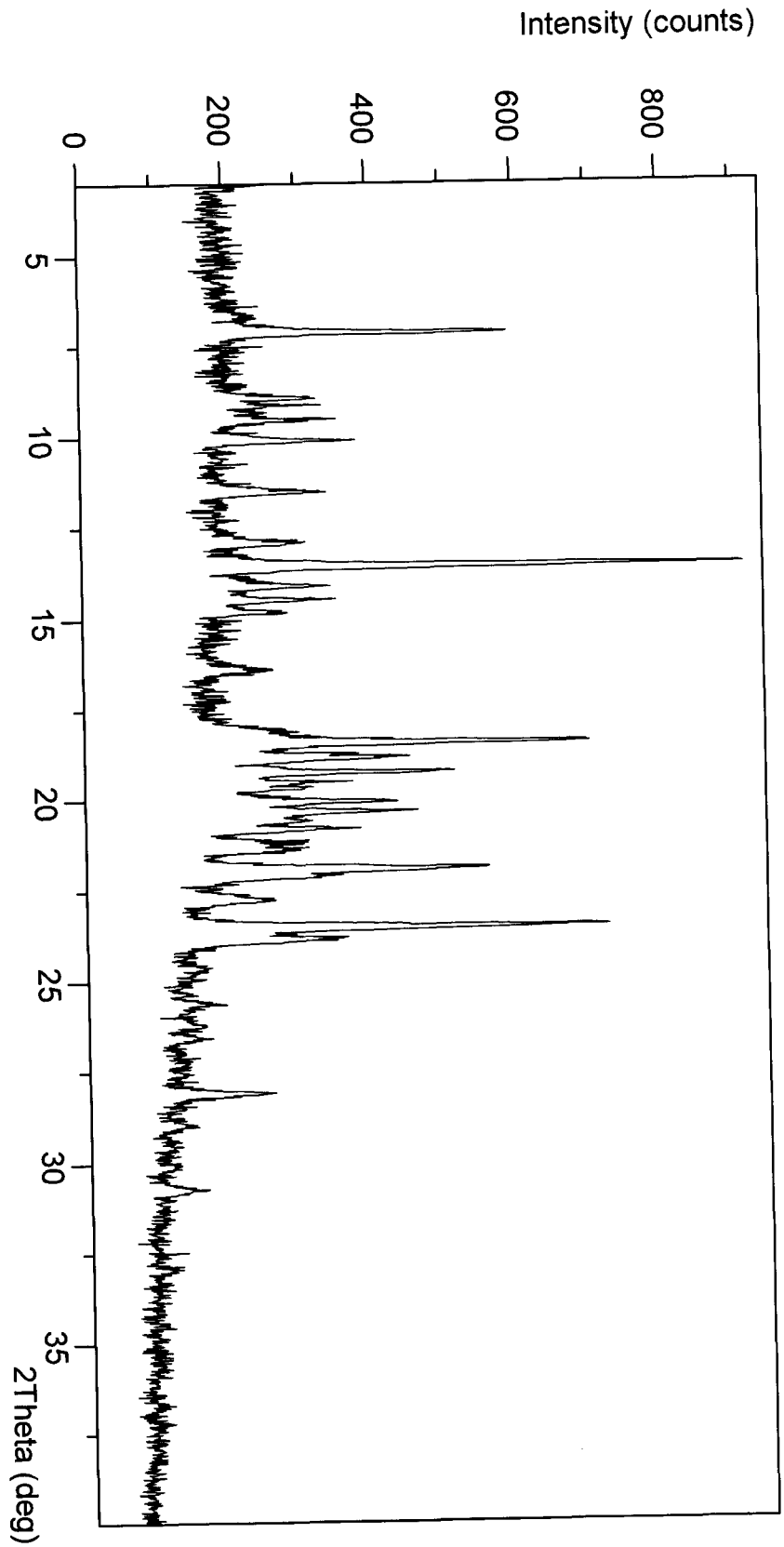


FIGURE 37. XRPD pattern of Form 17

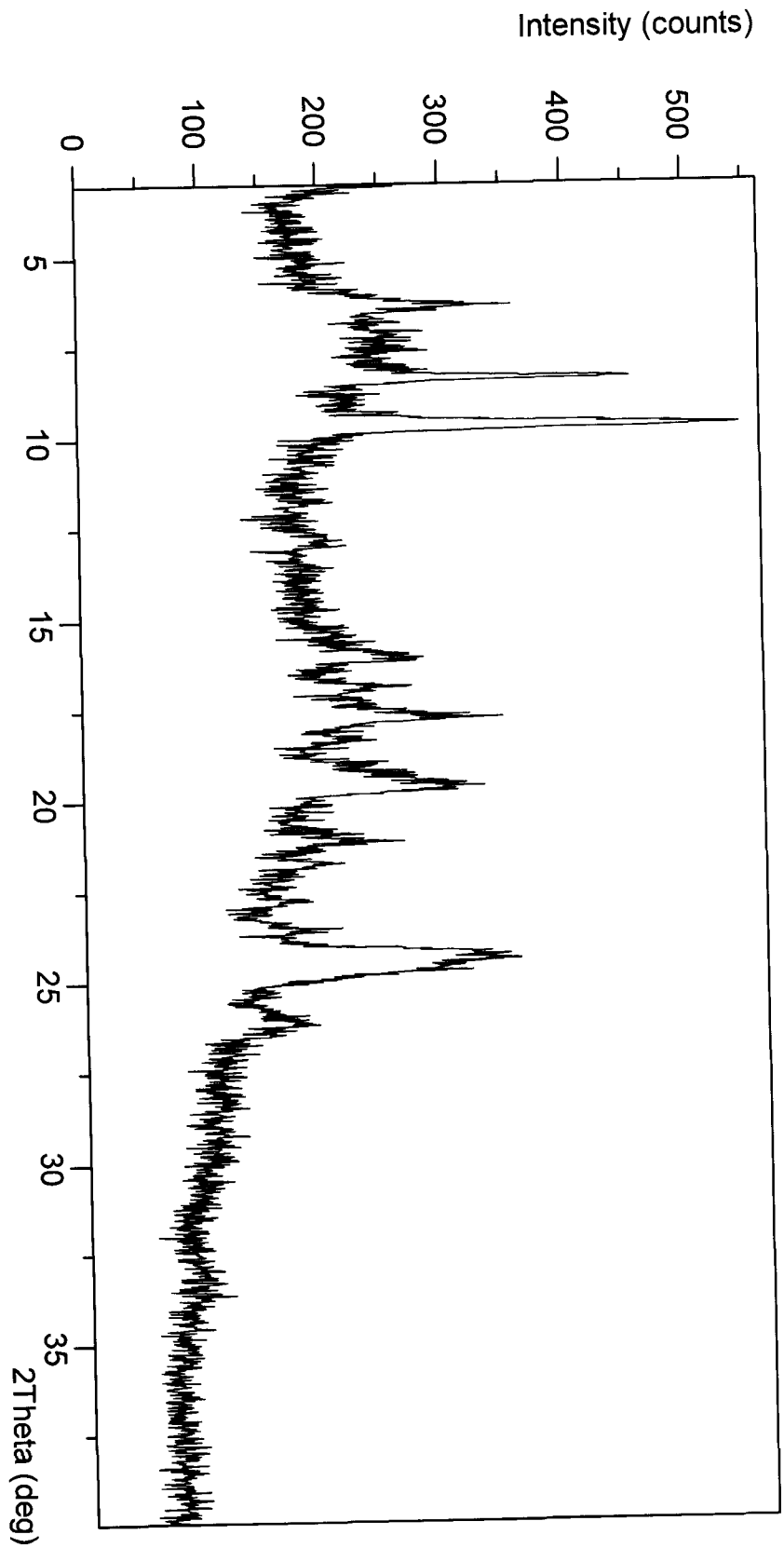


FIGURE 38. XRPD pattern of Form 18

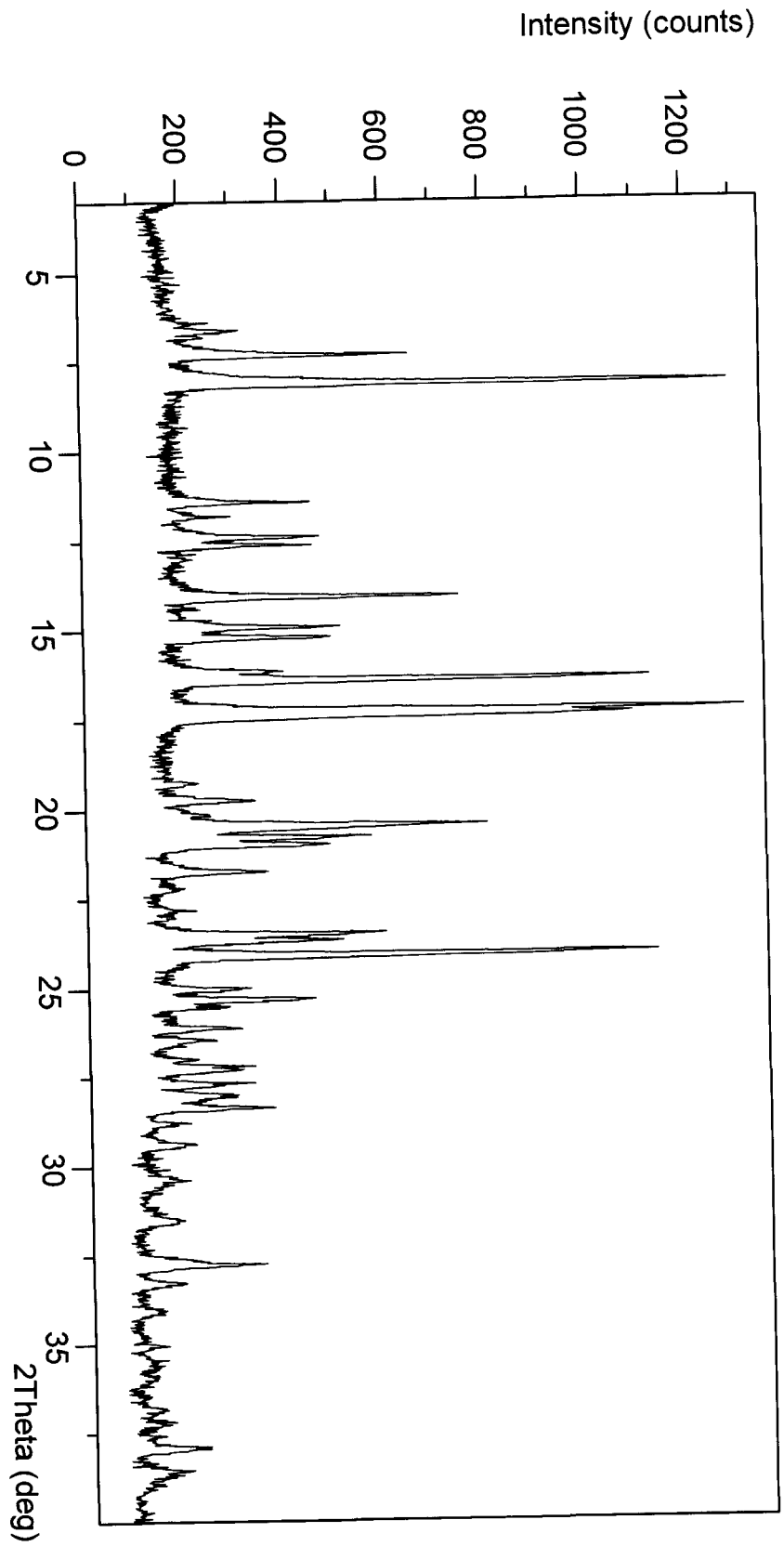


FIGURE 39. XRPD pattern of Form 19

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/CN2013/081170**

**A. CLASSIFICATION OF SUBJECT MATTER**

C07D 251/18(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

C07D 251/-; A61P 35/-

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNPAT, CNKI, EPODOC, WPI, REGISTRY(STN), CAPLUS(STN): crystal+, form, triazin, pyridine, cancer, isocitrate dehydrogenases

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2013102431A1 ((AGIOS PHARMACEUTICALS INC.)) 11 July 2013 (2013-07-11)<br>see compound 409 of description, pages 2, 75, 80-84 | 1-8 |
| A | WO 2010144338A1 ((ABRAXIS BIOSCIENCE LLC.)) 16 December 2010 (2010-12-16)<br>see the whole description | 1-8 |

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

| Date of the actual completion of the international search | Date of mailing of the international search report |
|---|---|
| **16 April 2014** | **30 April 2014** |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| **STATE INTELLECTUAL PROPERTY OFFICE OF THE P.R.CHINA(ISA/CN)**<br>**6,Xitucheng Rd., Jimen Bridge, Haidian District, Beijing, China**<br>**100088 China** | **KANG,Lei** |
| Facsimile No. **(86-10)62019451** | Telephone No. **(86-10)61648356** |

# INTERNATIONAL SEARCH REPORT

International application No.
**PCT/CN2013/081170**

**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☑ Claims Nos.: **8**
because they relate to subject matter not required to be searched by this Authority, namely:

[1] The subject matter of claim 8 relates to methods for the treatment of human body by therapy as defined in PCT Rule 39.1(IV). This opinion has been carried out on the basis of the subject matter of the use in manufacture of medicaments for treating the alleged diseases.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**INTERNATIONAL SEARCH REPORT**
Information on patent family members

International application No.
**PCT/CN2013/081170**

| Patent document cited in search report | Publication date (day/month/year) | Patent family member(s) | Publication date (day/month/year) |
|---|---|---|---|
| WO 2013102431A1 | 11 July 2013 | TW 201329054A | 16 July 2013 |
| | | US 2013190287A1 | 25 July 2013 |
| WO 2010144338A1 | 16 December 2010 | CA 2764785A1 | 16 December 2010 |
| | | AU 2010259002A1 | 12 January 2012 |
| | | KR 20120016674A | 24 February 2012 |
| | | EP 2440050A1 | 18 April 2012 |
| | | CN 102573485A | 11 July 2012 |
| | | US 2012238576A1 | 20 September 2012 |
| | | JP 2012529511A | 22 November 2012 |
| | | EP 2440050A4 | 03 April 2013 |